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THE LEUCOCYTE PICTURE OF THE BLOOD IN CASES OF PULMONARY TUBERCULOSIS, WITH A SPECIAL STUDY OF THE FILAMENT-NONFILAMENT COUNT

WINFIELD O. KELLEY

Fellow of the Trudeau Foundation, Trudeau Sanatorium, Trudeau, New York

Submitted for publication March 29, 1934

Since Ehrlich, in 1877, first made the discovery that he could divide the white blood corpuscles into neutrophilic, basophilic, and oxyphilic groups by the use of aniline dyes, many advances have been made both in the technical methods of staining and also in the interpretation of the total white-blood-cell and differential counts.

In 1904, Arneth (1), working at the Leube clinic, studied the nuclear structure of the neutrophiles and divided the cells into five classes according to the number of nuclear lobes. These as well as the lymphocytes and monocytes were subdivided until he had a total of 81 subdivisions.

It is obvious that a differential count made according to this classification would be difficult as well as time-consuming, and would require considerable training. Von Schilling (2) appreciated these difficulties after applying Arneth's method, and in 1920 published a simplified modification. He divided Arneth's Class I into three types: myelocytes, young forms, and band forms. All of the four remaining types of Arneth he included in his fourth type of segmented forms. In the study of acute infections the Schilling hemogram has been of definite value and has received widespread approval.

Pons and Krumbhaar (3) took another step toward simplification by dividing all neutrophiles into 3 classes: (1) Metamyelocytes (very young) with round or slightly indented nuclei; (2) Nonsegmented forms (young) in which the nuclear material is connected by broad bands; (3) Segmented forms (older) in which two or more groups of nuclear material are joined by narrow filaments.

Cooke and Ponder (4) also appreciated the difficulties of Arneth's method and found that inconstant results were obtained by its use.

They, therefore, evolved another method which they called the polymorphonuclear count. They put the polymorphonuclear neutrophile with an undivided nucleus in Class I. In Class II was placed the cell whose nucleus had divided into two lobes; in Class III the cell with three lobes, and so on to Class V. The nucleus never divides completely but always has a fine filament of nuclear material uniting the different lobes. Therefore, as a basis for classification, Cooke used the following criterion: "If there is any band of nuclear material except this chromatin filament connecting the different parts of a nucleus, that nucleus cannot, for the purposes of the count, be said to be divided." To the question, "Is the count accurate?" the authors reply that it has stood the acid test of time. They have shown that the percentage of error in their classification, when 50 neutrophiles are counted, is +0.09 and that a satisfactory count can be obtained when as few as 50 cells are counted.

Farley, St. Clair and Reisinger (5) based their classification upon the work of Cooke and Ponder, but with a further modification. The 5 classes were grouped into 2 classes, the first to be identical with Cooke and Ponder's Class I, and the second to include Classes II, III, IV, and V, thus dividing the polymorphonuclear neutrophiles into "nonfilament" and "filament" forms. Stated in simple terms, their count is the differentiation of 100 consecutive leucocytes to determine the percentage of nonfilament neutrophiles, filament neutrophiles, lymphocytes, monocytes, eosinophiles, and basophiles. In 190 presumably normal adults they found the average nonfilament count to be approximately 8 per cent and the upper limit of normal 16 per cent.

Mullin and Large (6) in their work used the classification as set forth by Farley, St. Clair and Reisinger, with one important modification. They based their observations on 100 polymorphonuclear neutrophiles counted and differentiated into filament and nonfilament forms. In 15 normal adults they found the nonfilament percentage to range from 8 to 16, with an average of 12.1 per cent. In cases of acute infection they pointed out that the filament-nonfilament count served as a valuable aid in determining the clinical picture of the disease, that it followed more closely the course of the infection than the total leucocyte count, and foretold complications in convalescence. Furthermore, they showed that in nonfilament counts of 50 per cent and

over, a very guarded prognosis must be given; in the majority of such cases the patients died.

In the following series of cases of pulmonary tuberculosis the classification of Mullin and Large was used for the purpose of deciding whether or not the filament-nonfilament count would prove to be of value in determining the activity of the disease, and perhaps the prognosis. However, attention was not given to the filament-nonfilament count alone, but to the total and differential leucocyte counts as well. Medlar's (7) interpretations of these counts were used as a working basis, although it was found desirable to make a modification which will be discussed later.

TECHNIQUE AND GENERAL PROCEDURE

In a study which involves making a large number of leucocyte counts at frequent intervals, it is essential that the method be as simple and rapid as possible and at the same time permit a fair degree of accuracy. With these principles in mind, Trenner automatic pipettes were used and specimens of blood were obtained from the finger with an automatic lancet—thus insuring a freely flowing drop of blood. The diluted samples were shaken for 2 minutes immediately after collection, and for 3 minutes just before making the count. The cells in four large squares in each of two counting chambers were counted and the average taken for the total leucocyte count.

For the differential counts, smears were made on no. 2 coverslips. At this point it must be emphasized that thin smears are essential for the proper evaluation of filament and nonfilament forms of neutrophiles. The slide method is entirely unsatisfactory and is not to be recommended. A clean coverslip was placed in contact with a small drop of blood from the finger; it was then drawn to one side, making a streak about 2 mm. wide. This was placed in contact with another coverslip and, as soon as the blood had stopped spreading, the coverslips were pulled apart in a direction perpendicular to the line of the original streak of blood, and in the same plane as that of the glass. The smears, stained with Wright's blood stain, were examined under high dry objective and no. 3 binoculars. For each count 200 white blood corpuscles were examined and classed as neutrophiles, lymphocytes (large and small), monocytes (including large mononuclears,

transitionals, and endothelial leucocytes), eosinophiles, and basophiles. During each count, 100 neutrophiles were also observed for the purpose of dividing them into filament and nonfilament types. The count was made across the film from one edge to the other in a line perpendicular to the direction in which the smear was pulled.

With a few exceptions all of the counts, both total and differential, were done by the author. All blood samples were taken between 8:45 and 10:00 A.M. Some patients were ambulatory and were able to come to the laboratory; others were in the infirmary. During the first ten days after the patient's admission to the sanatorium, four counts were made at 3- or 4-day intervals. Follow-up counts were then made at monthly intervals during the course of the study or until the patient was discharged.

This work included 111 cases in all of which a diagnosis of pulmonary tuberculosis had been made. One case was complicated with actinomycosis, another with pyelonephritis, 2 with pelvic symptoms of undetermined etiology, and one with a large furuncle.

As a basis for classification of the counts, Medlar's (7) standards were used (with one modification). In his "Mode for the normal leucocyte formula for the adult" he used the following figures:

Total leucocytes per cubic millimeter—6000 to 9000.
Polymorphonuclear neutrophiles—50 to 64 per cent, or less than 5000.
Lymphocytes—25 to 39 per cent, or more than 2000.
Monocytes—6 to 9 per cent, or less than 700.
Eosinophiles—1 to 3 per cent.
Basophiles—0.5 to 1 per cent.

In making interpretations it was found that the cells per cubic millimeter were more accurate than percentage values; therefore the former method of calculation was used. In cases of tuberculosis it was found more advantageous for us to shift the base line for neutrophiles from 5000 to 6000, thus making the septic picture as follows:

Total leucocytes—always above 9000.
Polymorphonuclear neutrophiles—always above 6000.
Lymphocytes—below 2000.

This combination indicates that ulceration of the tuberculous process is taking place.

Hyperplasia, or new tubercle formation, is indicated, according to Medlar (7), when the monocytes exceed 9 per cent or 700 cells. He gives as the hyperplastic picture the following:

> Total count usually within normal limits (never above 10,000).
> Neutrophiles—below 50 per cent.
> Lymphocytes—25 per cent or above.
> Monocytes always above 10 per cent.

The hyperplastic count was not a frequent finding in this study and is mentioned here only for the sake of completeness. There is indeed some disagreement concerning the rôle of the monocytes in tuberculosis (8). Some authors believe they appear not only during hyperplasia, but also during the healing of the tuberculous process, that is, when no tubercles are being formed.

Bredeck (9) shows that high monocyte counts may be of good as well as of bad prognostic significance in pulmonary tuberculosis.

On the other hand, Flinn and Flinn (10) state the following hypothesis:

> A high monocyte percentage, when accompanied by a normal or low lymphocyte percentage, suggests an active proliferative lesion. A rising monocyte percentage, when accompanied by a normal or low lymphocyte percentage, suggests an extension or exacerbation of the proliferative process, or a complicating extrapulmonary tuberculosis.

Cunningham, Sabin *et al.* (11) express the theory that "the tubercle bacillus attacks one type of cell, the monocyte, and that the complete analysis of the effect of tuberculosis on monocytes is a necessary factor for laying a firm foundation for progress in the study of this disease."

When the lymphocytes exceed 30 per cent, it is believed (Medlar) that the tendency is toward a healing stage. The monocyte-lymphocyte ratio as an index of healing has been emphasized by some workers (11, 12) whose reports may be consulted by the reader. Although this ratio may convey some valuable information, it has been found quite satisfactory to consider the numbers of each type of cell without any further calculation.

One of the problems confronting hemocytologists has been the reliability of the leucocyte count. The count does not give us direct information as does the x-ray, which shows the actual extent of pul-

monary disease, and the Gaffky scale which represents the approximate number of tubercle bacilli in the sputum. The abnormal leucocyte count is a response of the blood-vascular system to an infection in the living organism. It therefore *reflects* the pathological activity of the process without informing us as to the location or the exact extent of involvement. This response of the blood is nevertheless very delicate and often takes place before any of the grosser manifestations of disease occur. Indeed, this delicacy of response has caused some clinicians to question the reliability of the leucocyte count, since it is altered not only by mild infections but also by exercise, meals, and other factors. Sabin, Cunningham, Doan and Kindwall (13), in a study of normal individuals, found a wide daily variation of the total leucocyte count and also an hourly rhythm. More recently Kaminsky (14) has shown that exercise affects the leucocyte count in pulmonary tuberculosis, and has emphasized the value of making such counts under basal conditions. This factor was taken into consideration when the present study was undertaken. First, samples of blood were obtained from the ambulatory patients directly after breakfast, so that the only exercise taken was that in walking to the laboratory. For the infirmary patients, the exercise factor can be eliminated for purposes of the count. In order to determine whether or not a single leucocyte count could be relied upon, four counts were made on each patient during the first ten days after admission. The following is a comparison of the results obtained:

In a series of 111 patients on whom 4 admission counts were made at intervals of 3 or 4 days, the greatest maximum variation (that is, the difference between the highest and the lowest of the four successive counts) was 5,000 cells for the total leucocyte count, or 29.3 per cent. We also took the difference between adjacent counts (four for each case) and averaged these differences. These results on all 111 cases were then averaged and the figure 941 was obtained, meaning a 9.66 per cent variation. The same calculations were carried out for the neutrophiles, lymphocytes, monocytes, and nonfilament neutrophiles. Results showed that the variation for the monocytes was greatest (41 per cent for the average maximum variation). All the results are shown in table I.

As a supplement to these findings it may be said that the relatively

wide variations in the first four counts of some cases were actually trends in one direction, usually toward improvement. Chart I illus-

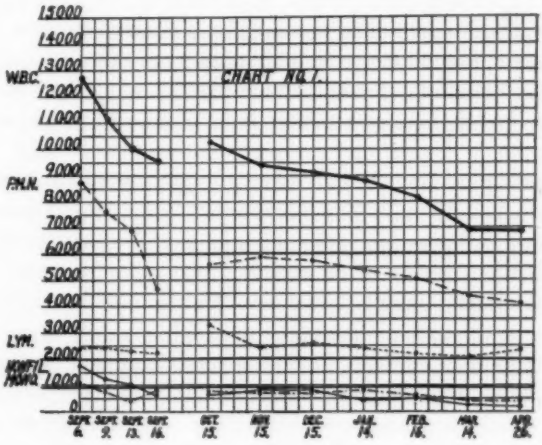
TABLE I

Comparison of first four counts after admission in 111 cases

	GREATEST MAXIMUM VARIATION		AVERAGE MAXIMUM VARIATION		AVERAGE DIFFERENCE IN ADJACENT COUNTS—AVERAGE FOR 111 CASES	
	Cells	Per cent	Cells	Per cent	Cells	Per cent
W.B.C.	5000*	29.3	1,983		941	9.66
P.M.N.	20	27.7	7.4	11 (67% basis)	4.15	6.2
Lym.	16	40	6.9	23.6 (25% basis)	3.69	14.7
Mono.	9	60	3.3	41 (8% basis)	1.89	23.6
Nonfil.	14	38.8	5.3	33.1 (16% basis)	2.72	17

* One case.

trates that, under intensive and careful treatment, the improvement which takes place in the short period of ten days will be demonstrated in the blood picture. Furthermore, since the leucocyte count is a



very sensitive indicator, many gastro-intestinal and pelvic disturbances, severe colds, and local infections may alter the count consider-

ably. Nevertheless, we may assume from the above that one count on any patient will be sufficiently accurate to be reliable.

It was with this hypothesis as a working basis that an attempt was made to correlate the hemocytological data with the other clinical and laboratory findings and to decide whether or not any additional information could be gained from such an investigation. The various topics will be discussed in the following order:

1. Comparison of the admission counts with x-ray, symptomatic activity, Gaffky Scale, and moderately coarse râles.
2. Special reference to neutrophiles, lymphocytes, monocytes, and nonfilament count.
3. Progress of patients:
   A. Comparison of blood counts with recommendations for treatment, x-ray findings and relapses.
   B. Illustrations of blood trends by comparison of case histories with leucocyte charts.

First, the admission counts on each patient were divided into "septic" or active and "inactive" groups according to the following criterion: If the total number of neutrophiles exceeded 6,000, the count was classified as "septic." It is obvious that some cases would not show a clear-cut "septic" or "inactive" blood picture, so that there might be one, two, or three "septic" counts, and the remainder "inactive." Nevertheless, we adhered strictly to the method of classification and correlated the results with some of the clinical and laboratory findings.

The cases were divided into three groups: "Minimal A," "Moderately Advanced A," and "Far Advanced A" according to the American Sanatorium classification. Of 25 "Minimal A" cases, 19 showed all four admission counts to be inactive, two cases had three inactive counts and one septic count. Of 4 cases which had three or four septic counts, three were complicated by stomatitis, tuberculous nephritis, or actinomycosis. In the "Moderately Advanced" group there were 75 cases, 30 of which had four septic counts, 9 had 3 septic counts out of four, 7 had 2 septic counts out of four, 7 had one septic count out of four, and 22 cases had 4 inactive counts. From these figures we can conclude that there is a slight tendency for the "Moderately Advanced A" cases to have septic counts. In the "Far Advanced A"

group there were 11 cases, 7 of which had 4 septic admission counts, and 4 of which had 3 or 4 inactive counts. Two of these last patients had unilateral pneumothorax at the time of admission, and although they were entered in the "Far Advanced" group they had no symptomatic activity and subjectively were feeling well. Therefore we may say that there is a great tendency for far advanced cases to show septic leucocyte counts.

Next, the blood counts were compared with the roentgenological findings interpreted in a special way by H. L. Sampson. He classified the pulmonary lesion as active or inactive, and for each of these groups made a note as to whether the process was predominantly exudative or proliferative. In the "active exudative" group there were 44 cases, 30 of which had 4 septic counts. In 5 cases there were 3 septic counts, in 3 cases, 2 septic counts, in 2 cases, one septic count, and in 4 there were 4 inactive counts. Summarizing these figures: Of the "active exudative" group 90 per cent had at least one septic leucocyte count. In the "active proliferative" group there were 11 cases. Of these 4 had 4 septic counts, one had 2 septic counts, in 2 there was one septic count and in 4 there were 4 inactive counts. In the "inactive exudative" group there were only 3 cases, one of which had 4 septic counts, one had 3 septic counts, and one had 4 inactive counts. In the "inactive proliferative" or most favorable group, in 3 there were 3 septic counts, in 4 there were 2 septic counts, in 7 there was 1 septic count, and in 34, 4 inactive counts. In this last group, therefore, in 77.5 per cent there were three or more inactive leucocyte counts. The agreement here is not more nearly perfect, (1) because pneumothorax interfered with the x-ray interpretation of activity and (2) because two of the patients had complicating factors which influenced the leucocytic response.

A correlation of the four admission leucocyte counts with the number of tubercle bacilli in the sputum (concentrated specimens) as represented by the modified "Gaffky Scale" (15) presented the following figures: There were 68 cases with negative sputum, 46 of which (67.6 per cent) had at least 3 inactive leucocyte counts. In all of the positive sputum group, irrespective of the Gaffky number, the great majority of cases revealed septic leucocyte counts. There were 43 cases ranging from Gaffky 1 to Gaffky X, of which 32 (74.4 per cent) had at least 3 septic leucocyte counts.

Next, the cases were divided into "symptomatically active" and "symptomatically inactive" groups determined by the presence of fever (99+ for men or 99.6+ for women) three times, or rapid pulse (90+ for men or 96+ for women) three times during the first seven days of the patient's residence at the sanatorium. Even though it must be granted that this method of determining the patient's clinical condition is somewhat unreliable, nevertheless we found a definite agreement between the symptomatic activity and the septicity of the leucocyte counts. Twenty-nine cases were classified as symptomatically active and 24 or these (83 per cent) had at least 3 septic counts. In the symptomatically inactive group there were 82 cases, 52 of which (63.4 per cent) had at least 3 inactive counts. It is safe to assume that the majority of those symptomatically inactive cases with septic leucocyte counts should be treated as cases of active tuberculosis, since it is known that active disease can exist without a marked elevation in temperature or pulse.

There has been disagreement concerning the importance of moderately coarse râles as a clinical finding in determining the activity of pulmonary tuberculosis. In spite of this disagreement moderately coarse râles were used as a basis for classification in this paper. Râles were present in 57 cases, 35 of which (61.4 per cent) had at least 3 septic leucocyte counts. There were no râles in 49 cases; 33 of these (67.3 per cent) had at least three inactive leucocyte counts. Five cases had questionable râles; two of these fell in the septic group, three in the inactive group. The agreement between these two sets of data is not striking, but is at least as close as might be expected, since it is known that râles may be absent in active tuberculosis, and then appear during convalescence.

Tables II and III correlate the numbers of lymphocytes, monocytes and the nonfilament count, with the inactive and septic counts. Briefly stated, the greater number of inactive counts showed the lymphocytes to be above 25 per cent or above 2,000 cells. The monocytes were usually below 9 per cent or below 700 cells. By far the best correlation was found with the nonfilament count which was most often below 960 cells or below 16 per cent.

In 41 patients having septic admission counts there is, however, some apparent disagreement. Although the lymphocytes fell below

25 per cent in most of the counts (indicating a lack of resistance), nevertheless, by absolute count the number of lymphocytes was below 2,000 in relatively few cases. This apparent discrepancy is explained by the fact that the total leucocyte count was high enough (often 10,000 or over) so that a count of even 20 per cent lymphocytes would necessarily place the absolute count at 2,000 or over. Table III also shows that monocytosis was not a frequent finding in the septic group,

TABLE II

43 cases with all four admission counts inactive

COUNTS	LYMPHOCYTES		MONOCYTES		NONFILAMENT COUNT	
	Above 2000	Above 25 per cent	Below 700	Below 9 per cent	Below 960	= to or below 16 per cent
All 4	18	28	29	23	40	35
3	7	8	6	11	3	6
2	7	5	5	6	0	1
1	6	2	1	1	0	1
None	5	0	2	2	0	0

TABLE III

41 cases with all four admission counts septic

COUNTS	LYMPHOCYTES		MONOCYTES		NONFILAMENT COUNT	
	Below 2000	Below 25 per cent	Above 700	Above 9 per cent	Above 960	Above 16 per cent
All 4	6	25	12	1	37	27
3	10	7	13	9	2	8
2	6	5	6	6	1	2
1	7	1	7	13	1	3
None	12	3	3	12	0	1

although the absolute number of monocytes did rise above 700 in 64 per cent of the counts. In the septic group the nonfilament count is again very significant. In 89 per cent of the counts it was above 16 per cent and above 960 cells in 94 per cent of the counts.

Since the nonfilament count showed the best agreement with the septic count which in turn agreed best with the x-ray activity classification, we correlated the nonfilament count with the x-ray activity. In the active exudative group there were 45 cases, 36 (80 per cent) of

which had at least 3, and 45 (88 per cent) at least one nonfilament count above 960 cells per cubic millimeter. In the active proliferative and inactive exudative groups there were only 12 cases which were quite evenly distributed and therefore did not compare in any definite fashion with the nonfilament count. In the inactive proliferative, or most favorable group, there were 54 cases. Of these 45 (83.3 per cent) had at least 3 nonfilament counts below 960 cells. Therefore it may be said that the nonfilament count is at least as reliable as the total polymorphonuclear count in determining, as far as we are able, the activity of tuberculous infection.

PROGRESS OF PATIENTS

Since one of the purposes of this study was to determine the value of the leucocyte count as an aid in deciding the treatment each patient should receive, we examined the type of count in relation to the treatment recommended and the results obtained.

There were 50 patients for whom infirmary care was recommended. Of these, 33 (or 66 per cent) demonstrated all four admission counts to be septic. Six patients had 3 septic admission counts, 4 had 2 septic counts, 2 had one septic count, and 5 had 4 inactive counts.

Cottage treatment without exercise was recommended in 55 cases. Of these 33 (or 60 per cent) had inactive counts on admission. Eight patients had one septic count, four had 2 septic counts, three had 3 septic counts, and seven had 4 septic counts.

Cottage treatment with exercise was recommended for 6 patients, 100 per cent of whom had 4 inactive counts on admission.

At the end of this study, or until the time of the patient's discharge the following conditions prevailed. Of 19 patients still receiving infirmary care, 13 (or 68 per cent) had septic leucocyte counts. Six patients were receiving cottage treatment without exercise; of these 4 (or 66 per cent) had inactive counts. Of 86 patients receiving cottage treatment with exercise, 78 (or 90 per cent) showed inactive leucocyte counts.

Concerning relapses, which were determined by the development of new infiltration or enlargement of cavity determined by the roentgenogram, we found that a large proportion of such relapses (71.5 per cent) occurred in the infirmary, and all of these patients (20) had septic

leucocyte counts. Four out of 5 patients having relapses under cottage treatment without exercise showed septic leucocyte counts, while only 3 patients with exercise had relapses and all of these had inactive leucocyte pictures. These figures indicate that patients with septic counts are in the greatest danger of relapse and must be watched most carefully.

Some authors have asserted that the leucocytes form such a sensitive indicator that they are more reliable than any other test in discovering relapses at their beginning. With this in mind a comparison was made of the dates when relapses appeared by roentgenogram and by the leucocyte count (determined by a definite increase of neutrophiles over the normal). Of 28 patients who relapsed, 22 (or 78.5 per cent) showed septic blood trends two to six weeks before the relapse appeared in the roentgenogram. These figures seem to support the above assertion, and argue in favor of routine, repeated counts in all cases of clinical tuberculosis whenever possible.

ILLUSTRATIONS

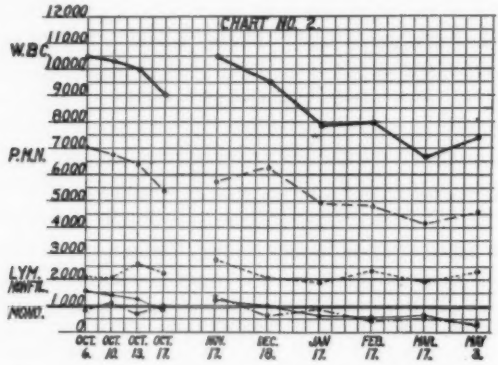
No attempt has been made to present a graphic description of all the cases studied, but a few typical cases have been selected to illustrate the blood trends found in the various types of pulmonary tuberculosis.

Case 1. White male, aged 20. Admitted to sanatorium August 31, 1932. Complaints: Loss of strength, slight pain in left chest, slight hoarseness, and some expectoration. Classified as moderately advanced tuberculosis, active exudative; symptomatically inactive; sputum negative; no râles heard. Progress: Treatment in bed until September 18, 1932, then up to meals, and graduated exercise up to 60 minutes on January 10, 1933. X-ray films showed continuous improvement. Temperature and pulse normal. No positive clinical findings except tubercle bacilli in the sputum, Gaffky I to III, on four occasions.

Chart 1. It will be observed that three base lines have been drawn; one at 6,000 for neutrophiles, the second at 2,000 for lymphocytes (these cells should be above this line to indicate good resistance), and the third at 960 for the nonfilament forms of neutrophiles. This chart illustrates first of all the variation in the first four counts; however, it will be noticed that there is a trend in one direction. At first the counts were septic, which agreed with the x-ray interpretation. The patient then showed an improvement in the leucocyte count which was accompanied by a definite amelioration of symptoms. Next, the chart shows the gradual improvement as healing of the tuberculous process was taking place. The neutrophiles

decreased in number and never rose above 6,000. The lymphocytes always remained above 2,000, indicating good resistance. The monocytes were slightly elevated for a time (possibly indicating some hyperplasia), then they finally fell below the 700 mark and remained at a low level. The nonfilament count was in keeping with the rest of the picture, being elevated above 960 for the first three counts and then decreasing to a normal count.

Case 2. Married white male, aged 29. Admitted to sanatorium October 1, 1932. Classified as moderately advanced A; active exudative. Sedimentation rate, 20 mm.; symptomatically inactive; no râles. Complaints: some pain in chest, cough ten times daily, no expectoration. Progress: Infirmary care from October 1, 1932 to January 28, 1933; pulse and temperature slightly elevated. November 7, 1932, x-ray revealed increase of infiltration on right with cavity more definitely outlined. Pneumothorax was begun on November 17, 1932. Only



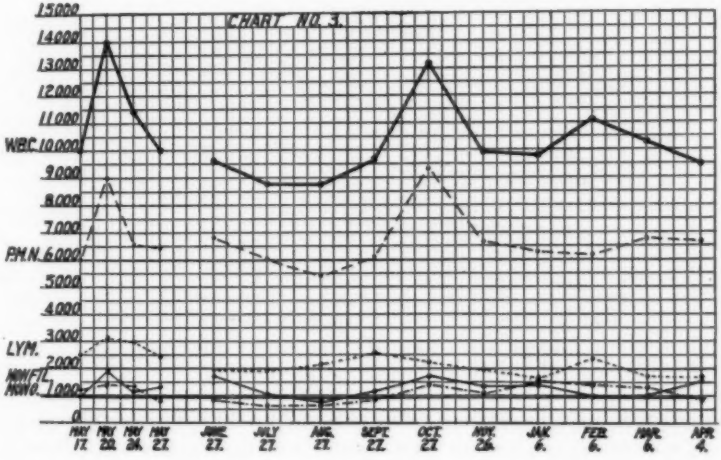
complication was development of a small amount of fluid which later disappeared. Sputum was positive for tubercle bacilli (Gaffky II) occasionally. Following pneumothorax, the patient improved symptomatically and gained 13 pounds in weight.

Chart 2. This shows a septic leucocyte count on admission but with the fourth count falling slightly below the septic level. The next two counts revealed a slight increase accompanying the extension of the disease. Then the counts returned to normal with improvement in the patient's physical condition. With two exceptions, the lymphocytes were always above 2,000, indicating good resistance. The monocytes were considerably above 700 during the early stages and relapse, then they decreased to a low count at the close of the study. The nonfilament count also was elevated at first, but later returned to a low level with the patient's improvement.

Case 3. Married white female, aged 31. Admitted to sanatorium May 6, 1932. Classified as moderately advanced A; active proliferative. Symptomati-

cally active as determined by the pulse; sedimentation rate, 29 mm.; sputum, Gaffky II. Complaints: Cough four times daily; some expectoration. Progress: The patient was given bed treatment in a cottage on admission. Because of lack of improvement, pneumothorax was begun June 21, 1932. Permission to walk to meals was given August 11 to October 16, 1932. The presence of fluid was noted by x-ray September 1, 1932. On October 13, 1932, x-ray revealed an increase of infiltration on the uncollapsed side. On November 17, 1932, there was a further increase with basal pleurisy. Patient had complained of cough and hoarseness which became very severe in October. Tubercle bacilli in the sputum rose to Gaffky V in July and remained between IV and VI during the course of the study.

Chart 3. This shows the first four leucocyte counts to be septic, in agreement with all the other clinical findings. There was some improvement in the blood

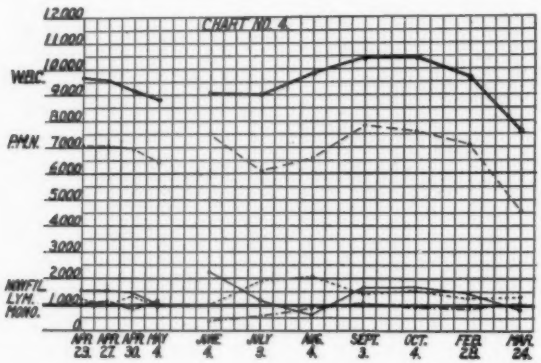


picture until September 27, 1932, when it became septic. Since then the counts have never returned to a normal level and in fact suggest an active focus of infection. The lymphocytes remained between 17 and 25 per cent, indicating only fair resistance; the monocytes were somewhat increased in number; and the nonfilament count was elevated almost constantly. This picture taken as a whole agrees with the course of the patient's disease and gives only a doubtful prognosis.

Case 4. Married white male, aged 43. Admitted to sanatorium April 14, 1932. Classified as moderately advanced A, active exudative; symptomatically inactive; sedimentation rate, 11.5 mm.; sputum, Gaffky, V. Complaints: Cough and expectoration and loss of strength. Progress: Infirmary care from April 23, 1932 to March 24, 1933. The patient had several frank hemoptyses May 15 and 16,

1932, followed by blood-streaked sputum for several days. X-ray taken May 29, 1932, showed increase of pulmonary infiltration on both sides. Sputum, Gaffky X on June 1, 1932. On June 7, 1932, pneumothorax was begun on the left side. July 14, 1932, fluid was present on the left. On October 4, 1932 the cavity appeared larger by x-ray and fluid had increased. The patient complained of frequent headaches and frequent night-sweats during her illness. At the close of this study she was still in the infirmary but was improving.

Chart 4. This shows the admission counts to be septic, in agreement with the other findings except symptomatic activity. The lymphocytes were very low, indicating poor resistance, and the monocytes and nonfilament forms were elevated. The blood picture remained septic for a long time and even became worse in September. The monocytes fluctuated somewhat but showed a tendency to remain elevated, indicating some hyperplasia or new tubercle formation. In

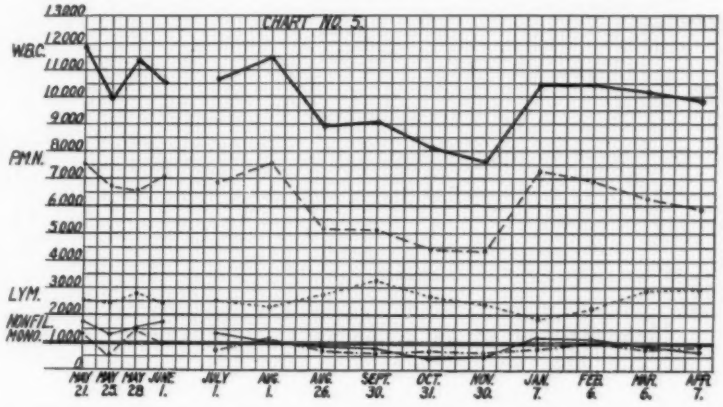


March, 1933, the count reached an inactive level for the first time, although the lymphocytes were still low and the monocytes high. At this time the patient was improving clinically but remained in the infirmary.

Case 5. Single white female, aged 26. Admitted to sanatorium May 12, 1932. Classified as moderately advanced A, active proliferative. Sedimentation rate, 20 mm.; symptomatically inactive; sputum negative. Complaints: Pain in chest, cough, and fatigue. Progress: Infirmary care from May 12 to October 8, 1932. Temperature remained normal but pulse rose to 100 occasionally. On June 24, 1932, x-ray revealed an intrapulmonary cavity on the left side. Sputum was Gaffky II from July to December, 1932. Sedimentation rate, 12 mm. July 18th. Pneumothorax was begun on left side July 19, 1932. Cavity had disappeared by September 15, 1932. On October 8, 1932, the patient was transferred to a cottage. On October 19, exercise was prescribed and thirty minutes twice a day was attained on November 19, 1932. On December 8, 1932, x-ray revealed a

pleuritic increase on the right side. The patient was removed to the infirmary January 14, 1933. Pulse rose to 96 and temperature to 100°F. often. On January 14, x-ray revealed increase of intrapulmonary infiltration and pleurisy on the right. Patient was treated in the infirmary from January to May, 1933, during which time she gradually improved both symptomatically and roentgenologically.

Chart 5. This shows the admission counts to be septic and correlates with the x-ray and sedimentation test. At the time of development of the cavity in June there was little change in the blood picture which had remained septic. From August to November, 1932, there was an improvement in the blood picture showing a decrease of neutrophiles, a rise in the lymphocytes, and a decrease of monocytes and nonfilament forms. At the time of development of the acute pleurisy a blood count was not made, but one shortly afterwards was markedly septic. After

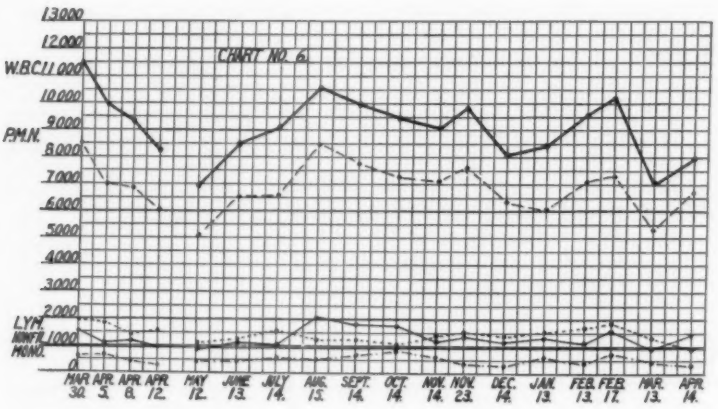


a short period the leucocyte picture improved and reached an inactive level in April. At this time the patient was improving clinically but remained in the infirmary.

Case 6. Married white female, aged 33. Admitted to sanatorium March 16, 1932. Classified as moderately advanced A; active exudative; symptomatically active; moderately coarse râles on left; sedimentation rate, 18 mm.; sputum, Gaffky VIII. Complaints: Pain in left chest, headaches, fatigue, cough 8 to 10 times daily, and expectoration. Progress: Bed rest in cottage March 16 to November 20, 1932. On March 31, 1932, pneumothorax was begun on the left side. X-ray film on April 15, 1932, revealed some adhesions on the left and fluid at the base. On June 6, 1932, the cavity appeared smaller. On July 21, x-ray revealed the development of a small area of infiltration on the right. Sputum decreased gradually from Gaffky X in July to Gaffky II in December, 1932. From November 26,

1932, to April, 1933, the patient was allowed to be up for meals but took very little exercise. She complained frequently of extreme fatigue and shortness of breath. Temperature remained normal but pulse rose to 100 occasionally. Weight gained, 10 lbs.

Chart 6. This shows the admission counts to be septic with decreased lymphocytes and increased nonfilament forms. Here we find agreement between the blood picture and all the other clinical findings. After a short period of improvement the blood count became worse in June, antedating the x-ray relapse by one month. Following this the counts remained septic almost continuously but did show some improvement toward the close of this investigation. The nonfilament

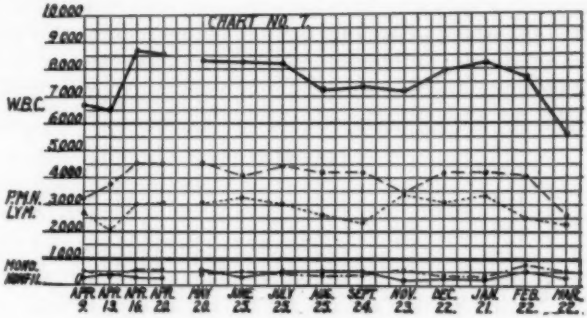


count remained high and the lymphocytes were always below 2,000; therefore we could give this patient only a doubtful prognosis on the basis of the blood picture.

Case 7. Single white female, aged 19. Admitted to sanatorium April 2, 1932. Classified as moderately advanced A (pneumothorax on right of 2 years' duration); symptomatically inactive; no râles; sputum negative. Complaints: Slight dyspnea on exertion and some hoarseness; no cough and no expectoration. Progress: Patient was given routine cottage treatment with exercise and continued to feel well.

Chart 7. This shows the typical inactive blood picture of apparently healed tuberculosis. The total leucocyte count remained within normal limits; the number of neutrophiles was always below 5,000; the number of lymphocytes remained high and almost reached the level of the neutrophiles which indicates that the patient had developed an excellent resistance. The monocytes and nonfilament count were always low. All of these factors point to a very favorable outcome.

Case 8. Single white male, aged 21. Admitted to sanatorium April 15, 1932. Classified as minimal A; active proliferative; symptomatically inactive; no râles; sedimentation rate, 19 mm.; sputum negative. Complaints: Patient "has to clear throat frequently." Progress: Cottage treatment without exercise from April 15 to July 15, 1932, then graduated exercise up to 45 minutes at time of discharge in September, 1932. This patient showed uneventful progress with continuous x-ray improvement. Weight lost, 9 lbs. Sputum was Gaffky II on one occasion, August 15, 1932.



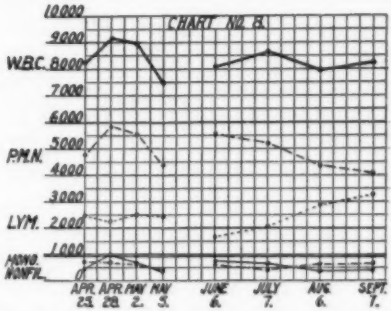


Chart 8. This shows the first four counts to be inactive although they do approach the septic borderline. The purpose of presenting this case is to point out the fact that it is not possible to fix any hard and fast rules for the interpretation of the leucocyte counts. There will be discrepancies sometimes between the various clinical findings and even between successive blood counts, and therefore clinical judgment is necessary in deciding upon the treatment of each case. It will be noted that for some time the neutrophile and lymphocyte lines were rather widely separated, then with the patient's improvement these lines approached each other, thus indicating excellent resistance and a favorable prognosis.

Case 9. Married white male, aged 25. Admitted to sanatorium June 30, 1932. Classified as moderately advanced A, inactive proliferative; symptomatically inactive; moderately coarse râles on left; sputum, negative. Complaints: None. Progress: Cottage treatment without exercise from June 30 to August 15, 1932. Temperature and pulse normal during this time. Weight gained, 5 lbs. On August 15, 1932, acute illness began with temperature to 104°F., pulse, 120 to 144, chills and profuse diaphoreses, abdominal discomfort and headaches. On August 19, 1932, x-ray revealed an intrapulmonary cavity which was probably present before. On August 20, 1932, spinal fluid examination showed 35 W.B.C. per cu.mm. On August 24th, x-ray revealed increase of infiltration (miliary) throughout both lungs. Sputum was Gaffky IV on September 14, 1932. Symptoms of severe toxemia continued and patient became increasingly weaker, then irrational, and finally unconscious. Death occurred at 2:30 A.M. October 7, 1932.

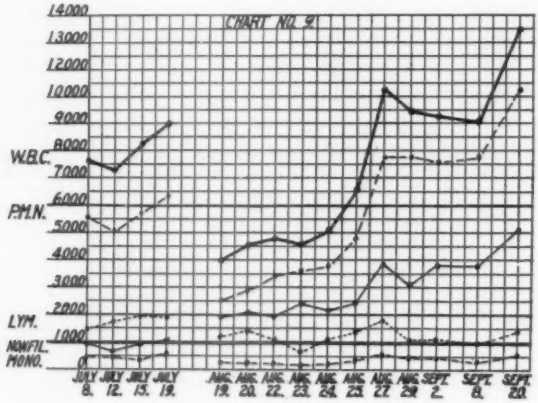


Chart 9. It will be noticed here that the four admission counts are only partially in agreement with the other clinical and x-ray findings. The neutrophiles approached the septic level and passed the borderline on the fourth count as did the nonfilament count, while the lymphocytes remained below 2,000. These factors gave the patient a doubtful prognosis, but did not predict the miliary dissemination which was to follow. At the time of onset of the acute illness the total leucocyte count dropped to a subnormal level of 4,000. The differential count revealed nothing striking until we came to the nonfilament count which was 77 per cent of the neutrophiles. This was therefore of the greatest significance and in fact suggested a fatal outcome. (Mullin and Large (6) state that a nonfilament count above 50 per cent is nearly always of bad prognostic significance.) This whole picture can be compared with that found in cases of ruptured appendix with rapidly spreading peritonitis and is explained by the fact that the hematopoietic system

is unable to respond to the unusual and sudden demand for great numbers of leucocytes. In a few days the blood forming organs had recovered partially, so that there was a gradual rise in the total leucocyte count and especially the neutrophiles. The nonfilament count continued to be elevated while the lymphocytes and monocytes remained at a very low level until death finally came.

CONCLUSIONS

In a series of 111 cases of pulmonary tuberculosis on whom repeated leucocyte counts were made it was noted that any single count is sufficiently accurate to be reliable.

The information obtained from a leucocyte count is of definite value in determining the clinical condition of a patient and in deciding the mode of treatment.

Tuberculous complications and other superimposed infections influence the blood picture to a great extent and therefore must be ruled out before any interpretation is given.

Since the leucocyte count is a very sensitive indicator and since it reflects the status of the tuberculous lesion quite accurately, repeated counts become very valuable in detecting relapses at their earliest stages.

The filament-nonfilament count, as applied to cases of pulmonary tuberculosis, has been reported for the first time in this paper. It has therefore been necessary to establish our own base-line for these cells which has been placed at 960, or 16 per cent of the neutrophiles. When the nonfilament cells exceed this number, they are nearly always an indication of septicity, and sometimes this count yields information that cannot be obtained by any other laboratory test.

BIBLIOGRAPHY

(1) ARNETH: Die Neutrophilen Blutkörperchen bei den Infektionskrankheiten, Jena, 1904.

(2) VON SCHILLING: Ueber die Notwendigkeit Grundsätzlicher Beachtung der Neutrophilen Kernverschiebung im Leukozytenbilde und über Praktische Erfolge dieser Methode. *Ztschr. f. Klin. Medizin*, Bd. 89: 1, 1920.

(3) PONS AND KRUMBHAAR: Studies in Blood Cell Morphology and Function. Extreme Neutrophilic Leucocytosis with a Note on a Simplified Arneth Count. *J. Lab. & Clin. Med.*, **10**, 1, 1924.

(4) COOKE AND PONDER: The Polynuclear Count. 1927.

(5) FARLEY, ST. CLAIR, AND REISINGER: The Normal Filament and Nonfilament Polymorphonuclear Neutrophil Count: Its Practical Value as a Diagnostic Aid. Phila., Pa.

(6) MULLIN AND LARGE: The Filament-Nonfilament Count: Its Diagnostic and Prognostic Value. *J. Am. Med. Assn. 97*, No. 16, Oct. 17, 1931.

(7) MEDLAR: An Evaluation of the Leucocytic Reaction in the Blood as found in Cases of Tuberculosis. *Am. Rev. Tbc.*, **20,** 1929.

(8) VOS: Die Monozytose bei der Lungentuberkulose. *Ztschr. für Tuberkulose*, **61,** 1931.

(9) BREDECK: The Schilling Blood Differential Count in Tuberculosis. *Am. Rev. Tbc.*, **20,** 1929.

(10) FLINN AND FLINN: The Leucocytic Picture of the Blood as an Aid in the Prognosis and Treatment of Pulmonary Tuberculosis. *Ibid.*, **20,** 1929.

(11) CUNNINGHAM, SABIN, SUGIYAMA AND KINDWALL: The Rôle of the Monocyte in Tuberculosis. *Bull. Johns Hopkins Hosp.*, **37,** 1925.

(12) DOAN AND SABIN: Monocyte-Lymphocyte Ratio. *J. Exp. Med.*, Suppl. no. 3, 1930.

(13) SABIN, CUNNINGHAM, DOAN AND KINDWALL: The Normal Rhythm of the White Blood Cells. *Bull. Johns Hopkins Hosp.*, Vol. 37, 1925.

(14) KAMINSKY: The Effect of Exercise on the Leukocyte Count in Pulmonary Tuberculosis. *Am. Jour. Med. Sc.*, Vol. 186, 4, Oct., 1933.

(15) BALDWIN, PETROFF and GARDNER: Tuberculosis, Bacteriology, Pathology, and Laboratory Diagnosis, p. 245.

DIABETES MELLITUS AND HYPERTHYROIDISM

The Report of a Case

R. G. HILLS, M.D., J. C. SHARPE, M.D., and L. N. GAY, M.D.

From the Medical Service of the Marburg Ward, the Johns Hopkins Hospital

Submitted for publication April 2, 1934

This case of diabetes mellitus complicated by hyperthyroidism is of interest because of the remarkable change in the carbohydrate metabolism which followed sub-total thyroidectomy. During the post-operative period there was marked inability to metabolize glucose and this could not be controlled even by the administration of massive doses of insulin.

E. B. (Unit History No. 45558) a white, married woman, aged 58, was admitted to the Johns Hopkins Hospital, September 27, 1932, on the service of Dr. Leslie N. Gay, complaining of fatigue, loss of weight, nervousness and diabetes. Her past health had always been excellent. She had had some dyspnoea occasionally on exertion and at times had noticed slight palpitation but no oedema. Menopause at 50 without unusual symptoms. She had eight children, all living and well.

Present Illness: For about three years, the patient had known that she had diabetes. On a restricted carbohydrate diet she had been well until about two months prior to admission (July 1932). She had occasional nycturia and voided on an average of three to four times daily. Her weight had decreased 5 lbs. Appetite had been very poor. She had had no polydypsia, polyuria or pruritus. Two weeks before admission, she had had eight remaining teeth extracted; abscesses were found at the roots of two. Since then she had seemed to improve.

The positive findings on *physical examination* are as follows: Height 4 feet 11 inches. Weight 130 lbs. Temperature 98.6°. Pulse 120, Respirations 16. The patient was a well nourished, well developed white woman of 58, who showed some evidence of recent loss of weight. There was no von Graefe, Stellwag or Möbius sign. The eye-grounds showed marked retinal arteriosclerosis. The thyroid was easily felt; both lobes were symmetrically enlarged, firm in consistence; the isthmus was thickened; no bruit or thrill. The heart was rapid in rate but regular; somewhat enlarged. Sounds of good quality; a short, soft, systolic murmur was heard, loudest in the aortic area and not transmitted. A-2 was greater than P-2. Blood Pressure: 150/65. The radial vessels were slightly thickened. The abdomen was quite relaxed, the recti widely separated. The pole of the right kidney was just

felt. Pelvic examination showed a third-degree tear with only slight rectal control remaining. The palms were clammy and cold and there was generalized sweating. No tremor of the out-stretched fingers.

Positive Laboratory Examination: Blood: hemoglobin 89%, R.B.C. 4,200,000, W.B.C. 4,200. Differential: polymorphonuclears 46%, small lymphocytes 50%, eosinophils 1%, large mononuclears and transitionals 2%; color index normal. Basal metabolic rate on admission +43. Blood chemical studies[1]—sugar 220 mgm. per cent, cholesterol 125 mgm. per cent, CO_2-combining power 55 vols. per cent. X-ray examination of the chest showed moderate enlargement of the heart with a non-tuberculous infiltration of both lung fields, probably secondary to the cardiac condition; no evidence of retrosternal thyroid. Urine: amber, S.G. 1022, acid, albumin 0, sugar 1 per cent, diacetic acid 4+. Microscopic: negative.

The patient was placed on a diabetic diet consisting of protein 60 gm., carbohydrate 100 gm., fat 100 gm., with insulin, 10 units three times a day. This diet was changed on several occasions, total fat being decreased until she was finally on a diet of carbohydrate, 100 gm., protein, 70 gm., fat, 50 gm. Insulin had been increased to 20 units three times a day. After six days, the blood sugar was 136 mgms. per cent and the patient was sugar-free. The basal metabolic rate at this time was +28, Lugol's solution was started and 0.6 cc. was given three times a day. Nine days later the basal metabolic rate was +20; the blood sugar was 139 mgms. per cent. The patient's condition improved a great deal while in the hospital. It was our impression at this time that she had a mild case of diabetes mellitus complicated by mild hyperthyroidism. Thyroidectomy was suggested but the patient declined operation. She was sent home on an 1800 calorie diet, with instructions to take Lugol's solution in small quantities and to report frequently for observation.

She was next seen on October 28, 1932; at this time her general condition was excellent. Her blood sugar was 147 mgms. per cent; the basal metabolic rate +8. Because of several insulin reactions of moderate degree, the insulin was reduced to 10 units three times a day.

The patient was again seen on November 29, 1932. At this time the blood sugar was 144 mgms. per cent, the basal metabolic rate +10. She had kept rigidly to a diet of 1800 calories and the urine was sugar-free. She had lost some 5 lbs. in weight since her first examination in September.

On February 28, 1933 the blood sugar was 129 gms. per cent and the urine free from sugar. However, she showed an increased enlargement of the thyroid, more marked tremor of the extended fingers, a higher blood pressure, further loss of weight and a basal metabolic rate of +18, in spite of the administration of Lugol's solution, 15 drops three times a day every other week.

She was next seen April 11, 1933. At this time her condition was fair, but loss of weight had continued in spite of a liberal diet. There was considerable tremor of the extended fingers. The eyes were normal in appearance, special eye signs

[1] Blood sugars were taken after fasting unless otherwise stated.

were absent. Blood pressure 190/70. Blood sugar 158 mgm. per cent. Basal metabolic rate +25. The patient was admitted to the Johns Hopkins Hospital April 11, 1933 to be prepared for thyroidectomy. Within twenty-four hours, on the same diabetic regime, the blood sugar was found to be 243 mgms. per cent. This increased hyperglycaemia, we felt, was due to apprehension and agitation. Operation was deferred for six days during which time an attempt was made to reduce the blood sugar. In spite of increasing doses of insulin, amounting to 80 units a day, the blood sugar failed to fall below 200 mgm. per cent. In view of her later experience, it is interesting to note that even before operation the patient was somewhat refractory to insulin. Since the thyroid condition seemed to be aggravated by worry, operation was performed April 19, 1933, and the greater part of a typical hyperthyroid struma was removed by Dr. William Rienhoff. The surgical post-operative convalescence was uneventful. The wound healed perfectly in five days and her temperature was never over 100°F., pulse not over 110.

Course of events from the first to the eighth post-operative day. After operation we at once experienced difficulty in controlling the diabetic condition. The patient was given 250 cc. of orange juice every four hours for twenty-four hours, with insulin varying in amount from 20 to 40 units; thereafter, a calculated diet of carbohydrates, 100 gm., fat, 50 gm., protein, 50 gm. The urine showed no diacetic acid but the blood sugar remained in the neighborhood of 300 mgms. per cent. It was thought that mild thyrotoxicosis was responsible for the inactivity of the insulin and Lugol's solution, 0.6 cc., was given three times a day. However, no improvement occurred; in fact increasing doses of insulin were necessary to control the acidosis that developed. On the 7th day, the blood sugar was 468 mgm. per cent and it was obvious that carbohydrate tolerance was decreasing in spite of the administration of Lugol's solution, which, therefore, was discontinued. It is interesting to add here that the intravenous administration of 40 units of insulin had not lowered the blood sugar at the end of half an hour. At this time, the blood chlorides were considerably below normal (310 mgms. per cent) and we thought that this might explain why the insulin had been ineffective.[2] Therefore, sodium chloride was given intravenously and by mouth.

Course from the ninth to the twelfth post-operative day. In view of the fact that large doses of insulin had no apparent effect upon the blood sugar even though the chlorides had returned to normal, it was decided next to reduce the insulin to 60 units a day. On the following morning, the patient's condition was worse. The temperature was subnormal, the pulse 110. She was listless and drowsy but could be aroused. There was loss of sphincter control. The blood sugar was 487 mgm. per cent, the CO_2 combining power was 25 vols. per cent. The patient was given 220 units of insulin in divided doses with 100 grams of glucose, some of it administered intravenously. No improvement followed and she was then given 10 grams of sodium bicarbonate by mouth. The following morning, the patient appeared

[2] Personal communication from Drs. Joslin and Harrop.

to be a great deal brighter and talked rationally. The blood sugar was 215 mgms. per cent and the CO_2-combining power 52.4 vols. per cent.

Course from the thirteenth to the twenty-second post-operative day. Because of an extraordinary diuresis, pituitrin, 1 cc., 2 cc. and then 3 cc., was given on three successive days and marked diminution of the urinary output followed which was accompanied by great clinical improvement. A diet of carbohydrates, 100 gm., protein, 50 gm., and fat, 50 gm. was again begun, but in spite of increasing doses of insulin up to 320 units per day, diacetic acid reappeared in the urine and the blood sugar increased to 460 mgms. per cent. The patient had now demonstrated repeatedly that she was unable to handle a maintenance diet no matter how much insulin was given. The only way the urine could be made free from acetone and diacetic acid was to administer at frequent intervals orange juice with large amounts of insulin.

Course from the twenty-third to the thirtieth post-operative day. On the evening of the twenty-third day, the patient expectorated a small amount of blood-tinged mucus, the pulse increased to 130, the temperature rose to 99.8° and a bronchopneumonia developed in the right upper lobe. The blood sugar was 528 mgm. per cent, the CO_2-combining power 11.7 vols. per cent. Intravenous glucose with doses of insulin totalling 685 units in 24 hours failed to bring about improvement. A transfusion of 500 cc. of citrated blood did not influence the refractory reactions to insulin. The hypernea, which had been present all day, became so much worse that during the night 40 grams of sodium bicarbonate were given intravenously. There was an immediate improvement and on the following morning the blood sugar was 268 mgm. per cent with the CO_2 combining power 68 vols. per cent. In the afternoon the blood sugar had fallen to 85 mgm. per cent. However, the improvement was only temporary; during the next twelve hours the blood sugar rapidly increased and a total of 890 units of insulin was required to hold it within normal limits. The bronchopneumonia together with an acute cystitis and sanguineous colitis undoubtedly played a part in defeating the action of the insulin.

Course from the thirty-first to the thirty-seventh post-operative day. On the morning of the thirty-first day, the patient abruptly developed an insulin shock with circulatory collapse. The blood sugar was 48 mgm. per cent. Glucose was given intravenously together with intramuscular injections of adrenalin and ephedrine. The blood pressure, which was very low, gradually rose to normal during the evening. Insulin and orange juice were then cautiously given and she was permitted to go through the night without further treatment. On the following morning, the blood sugar was 200 mgm. per cent and orange juice and insulin were again administered in small amounts. At midnight the blood sugar had increased to 340 mgm. per cent. During the night, 130 units of insulin were given in divided doses and at 8.00 A.M. the blood sugar was 70 mgm. per cent. During the day orange juice and insulin were given and the blood sugar remained below normal. The patient at the time was in a semi-stuporous state. She had frequent, involuntary, bloody stools. The pneumonia in the right lobe had almost entirely disappeared.

Neurological examination showed a right flaccid hemiplegia without facial involvement. It was thought that repeated vascular shocks in an arteriosclerotic person had caused cerebral thrombosis. Since the patient was unable to swallow, liquid nourishment was administered through a nasal catheter. During the next three days the patient received orange juice and raw eggs regularly with varying doses of insulin ranging from 110 to 320 units a day. Each morning she had a mild insulin shock. Aphasia came on at this time and also involuntary muscular twitching of the right arm and hand. The urine continued to show albumin, casts and numerous pus cells.

Course from the thirty-eighth to the fifty-seventh post-operative day. At this time it was apparent that the tolerance of the patient for glucose had greatly improved. This increase in tolerance coincided with the resolution of her pneumonia, the improvement of the cystitis and colitis and with the onset of hemiplegia. It was decided, therefore, to give her regular four-hour feedings consisting of 200 cc. of orange juice with two raw eggs and no more than 90 units of insulin a day. The blood sugar which had been 240 mgm. per cent was gradually reduced in the course of the next two weeks to 180 mgm. per cent. The symptoms of insulin shock no longer recurred. The patient showed remarkable general improvement. The blood pressure was 145/70, temperature and pulse normal, slight motor function had returned to her right leg, but the arm was still completely paralyzed. The aphasia had almost entirely disappeared. Since her second admission, 63 days before, she had lost only 11 lbs. The nasal tube was removed and the patient was put on a light diabetic diet, protein, 70 gm., fat, 100 gm., carbohydrates, 100 gm. with 100 units of insulin. The blood sugar averaged 160 mgm. per cent and sugar and ketone bodies disappeared from the urine. The patient was discharged on the sixty-seventh post-operative day, June 24, 1933, with the following diagnosis: diabetes mellitus; diffuse goitre with hyperthyroidism, thyroidectomy; moderate generalized arteriosclerosis; cerebral thrombosis; right hemiplegia and aphasia; bronchopneumonia; cystitis and colitis.

DISCUSSION

At the time of admission to the hospital, April 11, 1933, the patient had the symptoms of mild diabetes and mild hyperthyroidism. (1) It was known that she had had diabetes during the three previous years. The hyperthyroidism had come on apparently two months before the first admission. Twenty-four hours after the patient knew that she was to be operated upon, hyperglycaemia and ketonuria developed in spite of precisely the same diet and the same amount of insulin which had controlled the diabetes during the eight preceding months. Extreme fear had apparently precipitated an exacerbation of the hyperthyroidism and this in turn had caused a decrease of sugar

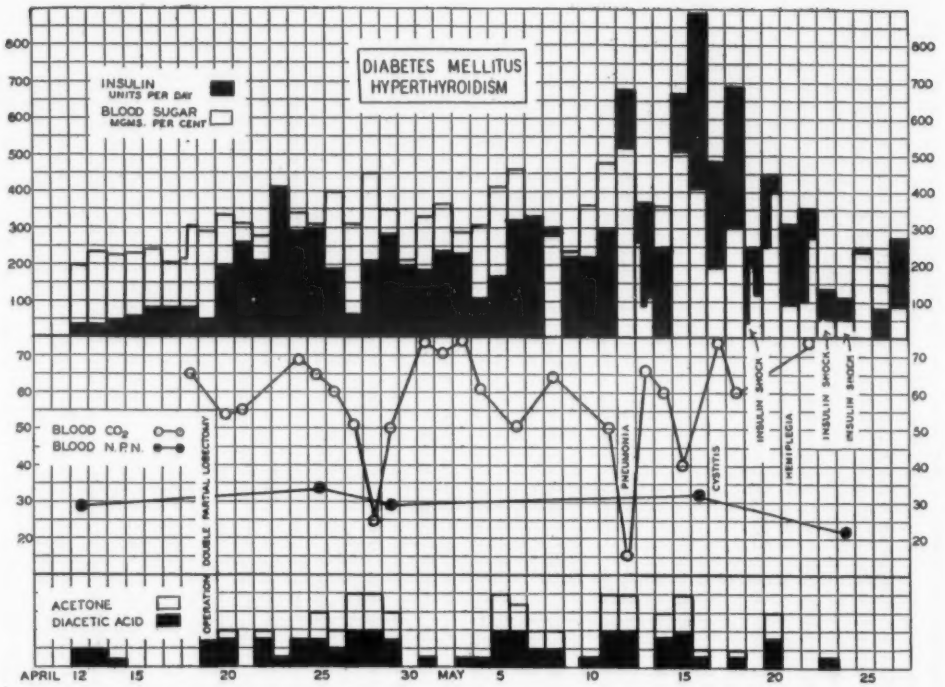


CHART I. REPRESENTATION OF THE RECIPROCAL RELATIONSHIP BETWEEN BLOOD-SUGAR VALUES AND INSULIN DOSAGE

The decrease in sugar tolerance immediately prior to operation (insulin dosage doubled); the relative ineffectiveness of insulin immediately after operation, and during the periods of complicating infections when 690 units of insulin were given in one day, is indicated. The variations in blood CO_2 and non-protein nitrogen, and the degree of acidosis is also given. After May 27, patient was regulated on dosage of 200 units of insulin daily with the blood sugar varying between 175 and 200 milligrams.

tolerance. (2) After six days of pre-operative treatment marked hyperglycaemia persisted, although the insulin dosage was doubled. Further delay seemed inadvisable and a subtotal thyroidectomy was performed. Following the operation, sugar tolerance became markedly decreased, necessitating the daily administration of 200 to 890 units of insulin. Lugol's solution given for four days was without benefit. Wilder (3) points out that it is often necessary to give iodine for a considerable length of time after thyroidectomy, especially to diabetics. Although a mild thyrotoxicosis often follows operation and causes an exacerbation of the diabetes, still we can find no reported instance requiring from 200 to 890 units of insulin a day. In the two cases reported by Andrus (4) only 100 units a day were necessary. In our patient apparently the action of insulin was in some way inhibited. It has been pointed out that a low sodium chloride content of the serum often inhibits the action of insulin, but in this instance there was no appreciable increase in the potency of insulin as the chloride rose to normal. Influenced by the work of Houssay and Biasotti (5), which suggests that there may sometimes be an extra-pancreatic origin of diabetes, namely, an excessive quantity of one of the anterior pituitary lobe hormones, we considered radiating the pituitary gland. An x-ray showed, however, that the sella turcica was smooth in outline and only slightly larger than normal. The onset of bronchopneumonia and a urinary tract infection produced a marked ketosis which necessitated giving huge doses of insulin—as much as 890 units in twenty-four hours. It is of interest that the intravenous injection of sodium bicarbonate brought about a dramatic subsidence of the acidosis. The sugar tolerance increased rapidly following the resolution of the pneumonia. However, vascular collapse and repeated insulin shocks were followed by cerebral thrombosis with hemiplegia and aphasia. After this stormy course, the patient gradually improved. Contrary to the experience of John (6), Joslin and Lahey (7), who point out that thyroidectomy lowers total metabolism and consequently improves the carbohydrate tolerance, our patient showed no improvement. She was refractory to insulin before the removal of her thyroid, but not until after the emotional disturbance precipitated by her decision to undergo thyroidectomy. When she left the hospital, twice as much insulin was required to control the

nitrogen, and the degree of acidosis is also given. After May 27, patient was regulated on dosage of 200 units of insulin daily with the blood sugar varying between 175 and 200 milligrams.

diabetes as had been necessary before the thyroidectomy. The cause of the ineffectiveness of insulin was never determined.

Supplementary Note: The general condition has improved up to the present time (February 28, 1934). The weakness of her right arm is less obvious and the patient is able to walk without assistance. The blood sugar, however, has remained elevated, averaging 260 mgm. per cent. Occasionally the urinary analysis shows a trace of sugar, but no evidence of acidosis. The patient is on a diet of carbohydrate, 145 gm., protein, 80 gm., fat, 70 gm., with insulin averaging 200 units in twenty-four hours.

BIBLIOGRAPHY

(1) Fitz, R.: Relation of Hyperthyroidism to Diabetes Mellitus. *Arch. Int. Med.*, **27**: 305–314, March 1921.

(2) Ginsberg, A. M.: Hyperthyroidism and Diabetes Mellitus. *Endocrinology*, **15**: 225–233, Dec. 1931.

(3) Wilder, R. M.: Hyperthyroidism, Myxedema, and Diabetes. *Arch. Int. Med.*, **35**: 736–760, Dec. 1926.

(4) Andrus, E. C.: Hyperthyroidism and Diabetes Mellitus. *Bull. Johns Hopkins Hosp.*, **1**: 383–393, June 1932.

(5) Houssay, B. A., and A. Biasotti: The Hypophysis Carbohydrate Metabolism and Diabetes. *Endocrinology*, **15**: 511–523, Dec. 1931.

(6) John, H. J.: Carbohydrate Metabolism in Hyperthyroidism. *Ibid.*, **11**: 497–578, Nov. 1927.

(7) Joslin, E. P., and F. H. Lahey: Diabetes and Hyperthyroidism. *Am. J. Med. Sc.*, **176**: 1–22, July 1926.

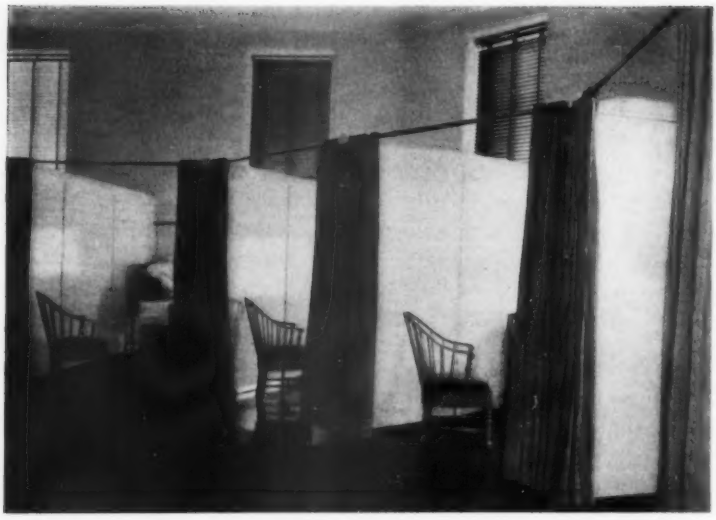
THE THAYER MEMORIAL EXERCISES HELD IN THE HURD MEMORIAL AMPHITHEATRE, FEBRUARY 24TH, 1934

INTRODUCTORY REMARKS

JUDGE HENRY D. HARLAN

President of the Board of Trustees of the Johns Hopkins Hospital

We are met this afternoon in honor of one who was long associated with the Johns Hopkins University and the Johns Hopkins Hospital, whose devotion to the interests and progress of both was deep and sincere, and whose fame as a physician, clinician and diagnostician is a part of our heritage. The last time I saw Dr. Thayer was when he stood in this place on the occasion of the formal dedication of the Hurd Hall and the Halsted and Osler Clinics, and in his own delightful way and with that charming diction of which he was so much a master paid tribute to Dr. William Osler, "the Chief" as he loved to call him. His untimely death in less than two months from that day, on December 10, 1932, saddened many hearts, and among his friends and associates there arose a strong desire to have in the Hospital some memorial that should fittingly perpetuate his name and add to the facilities for extending aid to the sick. It had long been recognized that one of the greatest needs of this Hospital, as of others, was provision for a class of patients whose means would not enable them to pay the fees and charges required for admission to the private wards for the purposes for which they were established, but who, on the other hand, could and were willing to pay for modest accommodations of a more private character than the public wards afford. It was known that Dr. Thayer had cherished the hope that provision be made at the Hospital for patients of gentle birth but of restricted resources who did not wish to enter the public wards, and for whom the rates in the private wards were beyond their means. At the time of his death, with the opening of the new Medical and Surgical Clinics, the old octagonal wards "D" and "E" were no longer needed for public ward purposes. The idea occurred to some of Dr. Thayer's



SHOWING ARRANGEMENT OF CUBICLES IN THE THAYER WARDS (OLD D AND E)

A CUBICLE. DIMENSIONS 9 FEET 6 INCHES BY 13 FEET

friends on the Staff that here was an opportunity to equip these wards with semi-private accommodations or cubicles for persons of modest means, meet a very pressing need, and establish a useful memorial to Dr. Thayer. The idea was approved by the Medical Board and by the Trustees of the Hospital. Upon the belief on the part of the Trustees that a large part, if not the whole, of the cost of the undertaking would be met by a fund to be subscribed by Dr. Thayer's associates, friends and former pupils, the improvement was undertaken, and has gone forward to completion. Director Smith and Assistant Director Houck have taken the greatest interest in the plans for the conversion of these old wards to semi-private wards. You are to have the opportunity of inspecting them immediately after the exercises in this room are concluded. You will see the character of the accommodations that patients of moderate means can get at a maximum charge of $5. a day, and with professional fees limited, on the suggestion of the Staff itself, to a sum not to exceed $150. in the aggregate. It is believed that these wards in effecting the beneficent purposes for which they are designed, will prove worthy of being named for Dr. Thayer, and will more than justify their existence. They have cost the Hospital with their equipment about $30,000. but towards this cost Dr. Thayer's friends have contributed about $11,000. and additional subscriptions are hoped for. In addition to an opportunity of inspecting the new Thayer Wards, one of which is for men and one for women, each having a capacity of 22 beds, you are to be privileged to hear something of Dr. Thayer himself from those who by knowledge, long association, friendship and affection are most competent to speak.

DOCTOR THAYER, THE TEACHER

JOSEPH S. AMES, PH.D., LL.D.

President of The Johns Hopkins University

It may seem anomalous to all of you that I should appear at all on this program today, where each one who speaks must refer in some way to Dr. Thayer and his work in connection with the Johns Hopkins Hospital. On the other hand, it is true that with the exception of Dr. Finney, it is probable that my acquaintance with Dr. Thayer covered more years than that of any man present, and I also had the

great pleasure of knowing him during this long period in many intimate ways. When I was invited to be one of the speakers on this occasion, I could not refuse, because I did wish to emphasize certain facts about Dr. Thayer and his relationship, both to the Hospital and to the University.

I congratulate the Committee which has been instrumental in raising funds for the reconstruction of the wards which now bear Dr. Thayer's name, because it seems to me that Dr. Thayer himself would be so immensely pleased to think that his name is associated permanently with a hospital group designed as these new wards are. The underlying purposes in the opening of these wards are, I believe, first, to take care of patients whose means are limited, but also to offer opportunities for private ward practice by a larger group of our younger practitioners in Baltimore who have previously been connected with the Hospital. I know of few things which would have interested or pleased Dr. Thayer more than these.

I knew Dr. Thayer as a physician and as an investigator, but I knew him best as a friend. I know nothing whatever in regard to his methods of teaching, nothing of the technique employed, but in spite of this, I am absolutely confident that Dr. Thayer was a great teacher of medicine. He had those fundamental qualities which are required of all teachers who earn and keep the respect of their students. His character was of such a quality that one can only speak of it as being ideal; he was thoroughly and absolutely unselfish. He was keenly interested in his students and in all young men, and of course he had a knowledge of clinical medicine second to none. He must, therefore, have been a good teacher. Furthermore, perhaps the essential requirement in a great teacher is that he should be a man of such a type that he inspires in his students the desire to be like him, and to follow his suggestions. Certainly Dr. Thayer was a man of this type. He illustrated also a certain attitude towards medicine which in my judgment is very essential. It is true that he was interested and extremely able in laboratory investigations. It is true that he became keenly interested in researches remote from the bed-side, but it is also true that every sick person who came under his attention received from him the care, the study, and the attitude of thought which made each of their cases a scientific investigation. When one speaks of sci-

entific medicine, of investigations in medicine, one is apt to associate the words with a laboratory. I think that Dr. Thayer proved that this was not necessarily true. I think the results of his life show that if a doctor considers each case which he attends as the subject of an investigation he must be regarded as being as much of a research man as one who is devoted to laboratory work. In the end, the center of thought in all medical work is the patient, is the sick man himself, and one of the great results of Dr. Thayer's teaching was to make this clear to all of his students.

DOCTOR THAYER, THE MAN

J. M. T. FINNEY, M.D.

Emeritus Professor of Surgery, The Johns Hopkins Medical School

My association with William Sidney Thayer, "Billy," as he was familiarly known to his close friends, began under very happy circumstances, just short of a half century ago. It hardly seems possible, but it will have been fifty years next Fall since I entered the Harvard Medical School, in September 1884. There, thrown with a group of other eager young men filled with enthusiasm at the idea of starting out on their life work, I was early attracted by one of them, a rather handsome, pleasant spoken, well-mannered youth who, by his frank and friendly attitude toward his classmates, was not long in securing their confidence and lasting friendship. Even at this early date, some of those charming little individual idiosyncrasies that later became a part of his very life, and served to amuse and delight his friends and to distinguish him from the common herd, had already begun to manifest themselves. He always appeared well groomed, immaculately dressed, a matter of some note among medical students in those days, perhaps so even today, not infrequently wearing a flower in his button-hole, which practice, as you all know, developed into a confirmed habit in later years. He was known to appear on occasion jauntily attired in cutaway coat, rather flashy tie, and spats, thereby creating a mild sensation, amounting even to a demonstration, in the class-room. But the characteristics that most impressed his classmates were his absolute detestation of everything that savored of sham or pretence, his insistence upon what he thought was right, and his transparent honesty in his work. He set himself studiously about

his tasks until he had thoroughly mastered them. He was no slacker, nor was he a bluffer. If he did not know a thing, he did not hesitate to say so. He never sailed under false colors. This characteristic trait of rugged, uncompromising honesty, so early and so prominently exhibited, manifested itself all through his life. The twin virtues of loyalty and honesty shared equally as the chief controlling influences in his life. They formed a large part of the rich heritage bequeathed to him by a long line of Puritan Ancestors, distinguished in New England annals of Church and State, ever since Revolutionary times. Never did cause or individual have more loyal, whole-hearted support, once he was committed to either, than that so freely bestowed by Billy Thayer upon those objects that he thought worthy. In all the years of our more or less intimate association, never did I hear him say an unkind word of anyone, nor have I known him to do an unkind deed, and there were times a plenty when ample provocation was not lacking. What greater tribute can one pay to another than to be able truthfully to say what has just been said? You friends of his assembled here, who knew him best, will, I am sure, bear me out in this assertion. There was no more delightful companion than Billy Thayer, always cheerful and optimistic. In spite of the great sorrow, which to most men would have been a crushing blow, that early saddened his married life, he was able presently, by sheer strength of character and will-power, to rise above the clouds of grief and, in a measure, regain his poise and become again his own delightful, cheery self, such as he used to be during Medical School and Hospital days. The supreme fortitude and courage, for it took these qualities in large measure, with which, responding to the call of duty, he bade good-bye to his desperately ill wife, well knowing that he would not see her again alive, and resolutely set out on the mission to Russia, showed the Spartan stuff of which he was made.

His friends always knew where Billy stood. He was incapable of dissimulation. He had definite convictions on all questions of public and professional interest, and was not afraid to express them when occasion required. While always ready to defend his position, whether on the popular side or the unpopular side it mattered not, he was never guilty of trying to force that opinion upon anyone. He was so constituted that instinctively he felt called upon to combat the wrong

that in his judgment needed resistance, as well as to defend the right that he thought needed assistance, and he was equally ready to do either with all his might. When challenged, he would throw his head back and to one side and elevate his chin (a very characteristic pose) and with an air of determination be ready to take on all comers.

In the Medical School, Thayer was a diligent student and painstaking worker in dissecting-room and laboratory. So insistent was he upon the neatness of his dissections, and such meticulous care did he bestow upon them and upon all of his other laboratory work, as at times to irk a bit some of his less conscientious and painstaking teammates. Work of this character, of course, did not long go unrecognized. It was no surprise, therefore, to anyone that Billy soon ranked high in his classes and stood well in the estimation of his teachers. Later when the appointments to the various hospitals were made, it was my great good fortune along with him to be appointed to the Resident Staff of the Massachusetts General Hospital. There, in the intimate contact into which we were thrown, I came really to know him and to love him, for no one who knew him could fail to love him. Full of the joy of living, the best of company, fond of song and story, and in those days a no mean performer in each, he added greatly to the atmosphere of good fellowship as well as of hard work that pervaded the House Officers' quarters. To this day, I recall with pleasure how enthusiastically we were regaled by him with the popular musical comedy hits of the day, along with others of his especial favorites, among which the "Bab Ballads," and "Micky O'Branigan's Pup" still stand out prominently in my memory. Billy's repertoire could hardly be described as classical. It was rather of the popular variety, which was better adapted to the tastes of his audience. He catered also to other more material tastes of the House Staff, for he especially prided himself upon his ability with the chafing-dish, and, by common consent, was voted chief cook of the Staff Flat. His specialties were Welsh rarebit, of which he was extremely fond, and scrambled eggs. Many a time, when returning to our quarters in the wee small hours, weary from long accident or emergency duty, were we cheered and refreshed by Billy's kindly ministrations in this respect, always so freely rendered. As a "House Pup," the term generally applied to members of the Resident Staff of the Massachusetts General Hospital

in those early days, Thayer exercised the same diligence and showed the same enthusiasm, even more so, if possible, that he had in the Medical School. His histories were taken and his physical examinations made with the utmost care. They were models of their kind, veritable works of art, made so by the lavish expenditure of physical and mental energy, and by the burning of the midnight oil. Rarely would he retire at night until the work for that day had all been done. He early showed that devotion to his patients' interests, which made them come to regard him not only as their doctor but their friend. This kindly interest in their welfare increased with the passing years.

Although he did not himself participate in them to any great extent, he was much interested in all out-door sports, especially baseball, which he had played in college, and in which he was a veritable fan. Like Dr. Welch, in former years, he could without hesitation give the names and records of all the well known players of his day. He greatly enjoyed a good prize-fight. Those were the palmy days of John L. Sullivan, who had been one of his boyhood heroes and of whose prowess, as a fellow-Bostonian, he spoke with pardonable pride. Billy's sporting proclivities took the form in later life of a great fondness for fishing during his summer vacation in the far West, and duck-shooting down on the shores of the Chesapeake and Back Bays. Here were to be observed the same fastidiousness in dress and the strict observance of the amenities of the occasion that characterized all his other actions.

Thayer had a keen sense of humor, which stood him in good stead in many a trying situation. Nobody enjoyed or appreciated a joke more than he, especially when it was at his own expense.

When the Johns Hopkins Hospital opened and Billy came down to join Dr. Osler's Staff, his joy and enthusiasm in his new work, new surroundings and associations knew no bounds. As he himself expressed it, he seemed "to be suddenly transported to a new world." So eagerly did he absorb new ideas and adopt new methods, so different from those to which he had been accustomed, that it did not take him long to become oriented and take his place as one of the leading and most popular and respected exponents of modern medicine, as exemplified in the person and teachings of Dr. Osler, his revered Chief, to whom, as is well known to most of you, his continued loyalty and devotion were touching in the extreme.

Thayer was a character that one can enthuse over. So many-sided, with so many interests; so strongly individualistic, and yet, at the same time, in certain things so conventional, he was, in many respects, unique. In speaking of him, it is difficult for one who knew him well not to indulge in superlatives. There was nothing petty or small about him. He was a great, noble soul, blind to another's faults and frailties, seeing only the good in one, kindly, helpful, generous, unselfish, lovable because so intensely human. In short, it could be said of him that in the truest sense of the terms, he was a Christian Gentleman, since he so well exemplified in all his actions the traditional virtues of each.

"And thus he bore without abuse,
The grand old name of gentleman,
Defamed by every Charlatan,
And soiled with all ignoble use."

These lines from Tennyson's "In Memoriam" would seem to apply with peculiar force to Billy Thayer.

In speaking of Thayer as a man, the word picture would be incomplete without some reference to one experience in his life that left a deep and lasting impress upon his character. A sure sign of strength in any man's character is first to be able to see his mistakes, and then to admit them and be man enough to profit by them. I have earlier referred to the exceptional hereditary background with which Thayer was favored. His home life, he states, was all that could be desired. He was reared in an atmosphere of culture and refinement. But notwithstanding all this, and incredible as it may seem to one who knew him only as he was in his later years, he, during a part of his college course, frittered away his time, wasted his opportunities, turned his back upon his early training and, to use his own words, "for a season trod the primrose path in company with other kindred spirits." Finally, the inevitable happened. He left college and spent a year in a distant city under the beneficent influence of an old schoolmaster, a clergyman friend of his father, whom Billy frequently spoke of and often quoted, always in the most affectionate terms, as the "Old Master."

Which, I wonder, is, after all, the more potent in the development of character,—Heredity or Environment? In Billy's case, ap-

parently the latter. Probably each played its respective part. Listen while I read the closing paragraph of a paper written by himself and which appeared in the "Harvard Graduate Magazine" for March 1923, entitled "Recollections of the Old Master,"—"Dear Master, time laid its hand on you softly and led you gently to the peace from which you fell asleep. To you age could never come. And in the heart of one of your old boys you live forever young. Nearly forty years have passed. He himself is older than you were when first your blessed influence came into his life. He has had his share of joy and sorrow, of success and disappointment. His share of success and happiness has been far beyond his desert. Whatever success and happiness have been his, whatever good he may have done in this world are in great part due to you,—to your example of courage and manliness and strength, of truthfulness and purity and simplicity, of tolerance and charity and love, of reverence for the past and confidence in the future, of consistent optimism—and to the great truth that you whispered in the ear of his conscience:

"The secret of eternal youth is enthusiasm"!

This, then, was Thayer's philosophy of life, the secret of his great success, as revealed by himself, namely, the devotion to an ideal. Is there not an object lesson here for us all? So deeply impressed had Thayer been by the character and example of the "Old Master," that unconsciously his own life had been transformed thereby, and became thenceforth a reflection of his Master's virtues.

In the passing of Dr. Thayer, his many friends and patients, by whom he was so beloved and who, in turn, meant so much to him; Harvard, his Alma Mater, which he served so devotedly and so long as overseer; the Johns Hopkins Hospital, where he did his best work and which he so dearly loved; his Profession, which he so signally honored; his Country, which he so enthusiastically served, all have sustained an irreparable loss. Humanity so enriched by his living is the poorer from his going.

It seems, therefore, peculiarly appropriate that these Wards which we now formally open for the care of people of moderate means, an object always so close to his heart, should bear his name.

DOCTOR THAYER—PHYSICIAN, SCIENTIST, COSMOPOLITAN

SIMON FLEXNER, M.D.

Director of The Rockefeller Institute for Medical Research

President Ames has spoken to you of Doctor Thayer as a teacher, and Doctor Finney as a man whom he had known intimately for fifty years—as a medical student and hospital interne in Boston, and as a medical resident and physician in Baltimore. I am privileged to attempt a brief portrayal of him as the distinguished and greatly beloved physician, scientist, and cosmopolitan whose European friendships played a significant rôle in his professional life.

My task, pleasant as it is, is rendered much simpler by the fact that Doctor Thayer has been in a sense his own biographer. In his occasional addresses[1] and writings he has told the story of the remarkable medical developments of his day in the United States, dealing with them from an introspective point of view which, to a discerning eye, reveals the growth of a personality, eager, thoughtful, idealistic, and sensitive to the high demands of a beneficent profession, of noble heritage.

I shall, therefore, endeavor to impart to you the impressions that I have received from a long acquaintance with Doctor Thayer and those acquired by a rereading of his writings, both general and technical. My friendship with Thayer extended over a period of forty years, since it chanced that we both entered the Johns Hopkins Hospital in the autumn of 1890, he to go into the "house" under Doctor Osler, and I into the laboratory to study pathology under Doctor Welch. For nearly ten years we were co-residents in the hospital—one in medicine and the other in pathology. We met regularly at the head table in the old, small, officers' dining room, and we were both influenced by the not infrequent presence at the table of that remarkable triumvirate of medical science and lore—Doctors Welch, Osler, and Halsted. On these banner occasions the talk was always lively and stimulating; and, may I remark, that even at ordinary times there was little talk of "shop." It is interesting to pass in mental review the

[1] Osler and Other Papers. William S. Thayer. The Johns Hopkins Press, Baltimore, 1931. I have quoted or paraphrased freely from this volume where the personal applications seemed unmistakable. S. F.

"officers" in my day sitting at that head table: Councilman, Thayer, Abbott, Nuttall, Mall, Barker, Frank Smith. The talk took a wide range; there was not a little good-humored banter. Thayer was already in the grasp of Anatole France, whose hold on his philosophy of life lasted until the end. Thayer quotes rarely in his miscellaneous writings, but among the few authors cited France leads all the rest.

Thayer came to Baltimore almost immediately after a year of study in Germany. There was a very brief interlude between the Boston interneship and the study abroad, filled by an essay into private practice which yielded little fruit. The chance opportunity to go to Baltimore was quickly grasped; this Doctor Finney has described. Probably the "Garden of Epicurus" had not been published, but a line or two in this favorite volume of Thayer's was anticipated. "In life we must make all due allowance for chance. Chance, in the last resort, is God." And it was chance that brought Thayer into relation with Doctor William Osler.

The manner of our first meeting is still vividly impressed on my mind. In the year 1890, the Ehrlich blood technique had only just been devised and published. Doctor Welch had received the small sheaf of students' dissertations describing the method, from his friend and co-worker under Cohnheim in Breslau, Ehrlich himself. These slim pamphlets were turned over to me with the suggestion that I master the methods and apply them to a case of leukemia in the hospital wards. To the student of clinical microscopy of today there is nothing particularly startling in this incident. But in my case it was pure adventure and exploration: the subtle, complex stains had to be prepared, the tricky film spreading and heating operations had to be acquired by trial and error processes; and the differential staining and counting were carried out without example, and wholly according to the sketchy, printed descriptions.

I was encouraged to present the amateur result at a meeting of the Johns Hopkins Hospital Medical Society, then in its infancy. After the meeting, an attractive young man, with a pained countenance, sought me out and asked where I had learned the blood technique. How searching that question was I soon learned, because Thayer began almost at once to apply the new methods of blood study, which he had acquired in his year abroad, either directly from Ehrlich him-

self or from one of his disciples. The possession of this technique soon brought eager young doctors to the clinical laboratories to study under Thayer, and in a short time it was being used widely throughout the country.

Thayer's first publication in the *Bulletin of the Johns Hopkins Hospital* is on a case of splenic-myelogenous leukemia, studied by this method. The date is 1901, and I fancy it is the first publication of the sort in American literature. I may say in passing that, in looking over the *Bulletin*, I find no record of my own amateur efforts with the Ehrlich technique.

The fact is worth stressing that during Thayer's year in Germany he should have acquired this new method of clinical investigation. It was a perspicacious act, and is the more remarkable since it is the sole material indication that he gave some of his brief time abroad to clinical studies. In the references in his writings to this year's work, the emphasis is wholly on pathology, which Thayer followed under Virchow. If he attended a clinic or was attracted by an eminent clinical teacher, he makes no mention of the circumstance. Hence the statement, made long after, that the laboratory year passed too fast; that he saw little of medicine; and that his object was to strengthen his foundation in one of the branches of natural science, which was beginning to be called on more and more in the effort to discover the nature and variety of manifestations of disease—becomes illuminating. While in the medical school and hospital, he spent much time in the pathological laboratory; so that the compelling attractions of clinical medicine, later to become so potent a force in his career, had yet to assert themselves.

As I have reflected on this circumstance in the light of later events, I have concluded that the explanation is to be found in Thayer's response to strong personalities among his teachers. The first to cast a spell over him was Reginald H. Fitz, the professor of pathology at the Harvard Medical School in the days when pathology was a branch of clinical medicine. In a memorial address made in 1913, Thayer said of Fitz: "His habits of discriminating precision in thought, in observation, in interpretation, in exposition, gave him that penetrating clearness of vision which enabled him to extract, as could no one else, from a mass of apparently unrelated observations, the concise,

clear, clinical picture correlated with definite physiological and pathological processes and anatomical changes." This was a combination of qualities in a teacher which Thayer appreciated; and notwithstanding a somewhat distant external manner, Thayer saw beneath the surface of this "careful and judicious temperament with a strong man's love for discussion, argument, opposition," which "stimulating qualities" incited his students "to keener and more efficient effort."

The example of Fitz, physician as well as pathologist, no doubt influenced Thayer in that fruitful German year. The clinical opportunities in Boston had surpassed the pathological; Thayer devoted himself, therefore, to the laboratory and neglected the hospital wards. The choice was to prove a wise one; probably under conditions very different from those which Thayer was soon to meet, it would still have been the best. But so far as predilection went at this time, given Thayer's particular temperament, there was no alternative. He was not projecting in imagination a distant future career; he was rather submitting to a compelling, immediate impulse. Pathology and practice were united in Fitz. Hence medicine to Thayer was already an opportunity to acquire and apply methods of precision, and the pathological laboratory was the obviously available place in which to see these methods applied to cases of disease.

The Ninth International Medical Congress met in Berlin that year (1890), and there Osler was pointed out to Thayer—"a figure which stood out from all the rest." This sentence is written with almost prophetic fervor. Well might the alert figure with Celtic features, drooping moustaches, and small, nervous hands, the physician-in-chief of the richly endowed, newly opened Johns Hopkins Hospital, arrest the young man's attention. "How much of Osler was in that first glimpse," he wrote long afterwards, "Of how little was I conscious at the moment. How little did I fancy that in three months I should be sitting at his table, and that to him I should owe so large a part of the blessings of my life!"

"Not for nothing one face, one character, one fact, makes much impression on him, and another none. This sculpture in the memory is not without pre-established harmony. The eye was placed where one ray should fall, that it might testify of that particular ray."[2]

[2] Essay on Self-reliance. Ralph Waldo Emerson.

Thayer, the physician, begins at this point. The laboratory with its special problems, the master with his own time, removed from the world of distracting human relations, the practitioner and the unsoundness of medical practice—all recede quickly into the background. The start had been a false one; there was to be a rapid reversal of ambition. Thayer had again fallen under the dominance of a gifted, rich, and strong personality, this time one closely attuned to his own vibrant nature.

Two infectious diseases were rampant at that time in Baltimore—malaria and typhoid fever. Thayer's studies in the clinical laboratory were directed toward malaria, for which his knowledge of blood technique especially qualified him. The discovery of the malarial parasite by Laveran ten years earlier had already been confirmed in America by Councilman and Osler. The Italians especially were making rapid advances in the delineation and interpretation of the parasites themselves. Thayer's investigations with Hewetson fitted into and enlarged this expanding subject; and Thayer's "Lectures on Malaria," superbly illustrated and published in 1897, carried the new knowledge throughout the English-speaking world. Before long, such erroneous and confused diagnoses as "typho-malarial fever" and the like were driven more and more into remote parts of the land, as laboratory diagnosis with the microscope came to supplement clinical observation of patients. This notable instance of the two complementary parts of the modern clinic, functioning in harmony, became the model on which Thayer ever afterwards based his belief in and teaching of the scientific regeneration of medical practice.

A first vacation was taken in the woods. A year before when he left the laboratory he was wretched; now he was carefree and happy. "What had happened? Old notions of mathematical accuracy, of science *versus* art, *etc.*, which had so disturbed him—how small they seemed. And medicine presented to him a wonderful opportunity, based on fundamental science, for the aid of which he was reaching out more and more every day. What a fascinating problem the art of medicine is. How little he had grasped the significance of the human side of medicine."[3]

[3] The Medical Education of Jones. Osler and Other Papers. William S. Thayer. The Johns Hopkins Press, Baltimore, 1931, page 71.

Success had come. Thayer had learned much from his "chief," as he gladly acknowledged. He made few enemies and many friends. In the midst of discord, he aimed to live in peace. He looked not for the selfishness, pettiness, and ingratitude, but rather for the kernel of sincerity, idealism, and beauty that lay hidden in human beings. The world, he found, was a better world than he had fancied.

With this philosophy to sustain him, Thayer became in time a virile force in medicine in the United States. His contributions to medical literature were notable. He made many addresses, and he was distinguished with the presidencies of the Congress of American Physicians and Surgeons, and the American Medical Association. The medical profession honored him, attended to him, and was influenced by his words.

"Twenty-five years have passed by. Great changes had taken place in medicine. Through the introduction of procedures, diagnostic and therapeutic, based on the application of the fundamental sciences, remarkable advances had been made in the art and science of medicine. Researches in no way inferior to those carried on in the laboratories of the fundamental sciences were being pursued by members of the clinical staff."[4]

With this advance, Thayer detected a regrettable tendency against which he warns: "A sound basis in the fundamental sciences, so desirable for the trained and scholarly physician, is in no way a *short cut* to experience, practical and human, which always has been and always will be necessary to make a good diagnostician, a good doctor, and a good clinical teacher."

He reiterates the teaching of Hippocrates: "Look for that which may be seen, felt, heard, which may be appreciated by sight, by touch, by hearing, by the nose, by the tongue, and by the powers of reason; in a word, all that can be discovered by such powers of appreciation as we possess."

"The power to explore is to my mind a great part of the art." This Hippocratic aphorism, quoted on the title page of Laennec's treatise on auscultation, Thayer adopted almost as a motto.

He deplored, therefore, that so large a proportion of American

[4] The Medical Education of Jones. Osler and Other Papers. William S. Thayer. The Johns Hopkins Press, Baltimore, 1931, page 77.

and foreign physicians are sadly lacking in the essential foundations of a training in diagnostic methods, and he warns against a growing tendency to substitute laboratory reports for clinical observation and tests. He speaks sadly of them as traps into which practitioners fall in too many instances, and calls them "liabilities" often, rather than helps. He insisted that interest in bacteriological, serological, and chemical tests, indispensable as they are, and the newer physical methods of exploration, should not lead us to forget the necessity of prolonged and systematic training in laboratory, ward, and outpatient department, in pathological anatomy and in physical diagnosis, in auscultation and percussion.

Thayer had passed from the ward and the lecture room in the medical school and hospital to the rostrum of the medical profession of the land, and his voice was listened to eagerly at home and abroad.

Thayer was no chauvinist. He had seen medical education in the United States grow from a simple, incomplete, sadly inadequate state to a strength well in keeping with the strong system abroad. But nevertheless he advised the aspiring medical student to go to Europe today, as he used to do fifty years ago. "Make the acquaintance of men and methods in other parts of your own country and in other countries. A period of time spent in a foreign city, sufficient to give one an insight into the language and habits, and ways of the people, and especially to give one an acquaintance and association with one's colleagues in a foreign country, is of great value. Go to large medical meetings in this and other countries whenever you have the opportunity. There is no more valuable experience than that of making acquaintance of students whose communications you may have to read. Osler's advice to all his students used to be to become peripatetic doctors."[5]

These are morsels of advice which Thayer offered his students and the medical profession; and he practised what he preached. His acquaintance in France and England was large and notable; he knew in a friendly and even intimate way the medical élite of those countries. He attended medical gatherings large and small, participating in their deliberations, and became a symbol of the internationalist,

[5] Scholarship in Medicine. Osler and Other Papers. William S. Thayer. The Johns Hopkins Press, Baltimore, 1931, page 224.

in the best sense, among teachers and practitioners of medicine. His commanding position among his colleagues at home is shown by the fact that he became the consultant of the elect among them.

And Thayer cultivated avocations as well as a vocation. His nature was diverse and many-sided. He scarcely needed the advice given by Osler to the McGill students: To begin at once to acquire some interest—an outside hobby—other than purely professional ones. Thayer found solace and refreshment in the woods; he wooed the muse of verse, and he found intellectual relaxation and stimulation in the history of the great diagnosticians of the 18th and 19th centuries—the men who, by technical devices and intellectual perspicacity, had advanced the art of medicine which Thayer so much loved to contemplate. Thayer has provided the historical setting for his biographical explorations.[6] They begin with Morgagni's "Seats and Causes of Disease Investigated by Anatomy," which appeared in 1760, the forerunner of and foundation on which Auenbrugger, Laennec, Addison, and Bright built their enduring fame. They, with Jenner, Bell, Johannes Müller, Beaumont, Claude Bernard, Pasteur, Virchow, Koch, and Ehrlich became subjects of contemplation and emulation to Thayer. Small wonder, therefore, that he was chosen to make memorable centenary addresses abroad on Laennec, Bright, and Pasteur.

Thayer loved to point out that in 1789 the Dictionary of the French Academy defined medicine as "a conjectural art," in contrast with the definition given by Littré one hundred years later: "the art which conserves health, cures the sick, and is founded on the science of disease or pathology." Here indeed is progress!

Candide's maxim: "Cultivons notre jardin" is found repeatedly in Thayer's writings.[7] This wise saying might well be his epitaph, for with the "needful illusions,"[8] considered indispensable by his master, Anatole France, Thayer grew many flowers of imagination, kindliness, and friendship in his garden. He dispensed them freely and even spread them in the path of students and practitioners in high and in

[6] Self-education under Guidance. Osler and Other Papers. William S. Thayer. The Johns Hopkins Press, Baltimore, 1931, page 230.

[7] The University and Medicine. *Ibidem*, page 315.

[8] Garden of Epicurus. Anatole France.

humble places; he heaped them on his patients, rich and poor alike. Thus among all the trials and perplexities of a distempered world, he remained of firm faith in the future and a confirmed optimist.

In 1927, The Thayer Lectureship, in memory of his wife and himself, was formally inaugurated. There were complimentary speeches to which Thayer responded. He summed up his professional life in carefully chosen words, from which I quote:

"I cannot tell you how happy I am that you should have made this a lectureship in clinical medicine, to which most of my life has been given. You may not know that at the beginning of my career and for many years afterwards, my desire was not to be a clinician, but a pathologist. My one wish at that time was for opportunity to work on special problems in the laboratory." This early attraction for the laboratory remained alive in Thayer's mind. "Doctor," said one of the boys, "Have you read 'Arrowsmith?'" "No," said Jones, "I have not, but I will." He read it and lay back in his chair and laughed. "By Jove," said he, "I might almost have written that myself twenty-seven years ago."[9]

Thayer had reached out in his youth for almost mathematical certitude in medicine, and his disappointment with the clinical fare set before him drove him into the pathological laboratory. It is, therefore, logical that he should himself have played so distinguished a rôle in applying the rapid advances of knowledge to the art of medicine itself. He was fortunate beyond most men in the circumstances of his intellectual development; and it is a tribute to his aptitudes and to his simple modesty that he gained so much and took to himself so little.

He met his last days with calm philosophy, of which his life was an example. Too intelligent and experienced to be deceived by his physical state, he aimed to disarm apprehension in his friends and spare them the knowledge of his pain and imminent destiny. His last evening was one of intellectual, social companionship, and when the summons came he met it, as he had met other personal crises, with fortitude and acceptance. "This is the end."

[9] The Medical Education of Jones. Osler and Other Papers. William S. Thayer. The Johns Hopkins Press, Baltimore, 1931, page 83.

GLYCOGENETIC FUNCTION OF THE LIVER IN EXPERIMENTAL HYPERTHYROIDISM[1]

MARY V. BUELL AND MARGARET B. STRAUSS

From the Cardiographic Laboratory and Chemical Division, Department of Medicine, the Johns Hopkins Hospital, and the Johns Hopkins University, Baltimore

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INTRODUCTION

The lactic acid content of both cardiac and skeletal muscles of normal and of thyrotoxic animals has been extensively reported by Andrus, McEachern (1–5), and their coworkers. They found the lactic acid content of both of these tissues to be significantly greater in the thyroxinized than in the normal animals. In fact, they found, "the lactic acid content of the cardiac muscle is seen to be almost doubled in the thyrotoxic group" (1). Andrus interpreted his observations as follows: "It appears, therefore, that the metabolism of carbohydrate in the presence of hyperthyroidism is at fault less in the ability of the organism to store carbohydrate than in the abnormally rapid break-down of glycogen" (2).

Quite at variance with these results and interpretations were the observations of Buell, Strauss and Andrus (6), who concluded, "In gastrocnemii from severely thyroxinized animals lactic acid formation is *inhibited*, as evidenced by lower initial values, slower rate of formation, and earlier cessation of production than in the normal. Decreased glycogen is not the cause of decreased lactic acid production." The latter authors were not misled, as were the former, into interpreting single, isolated, "resting" values for lactic acid, which must be conditioned by many factors, both technical and physiological, but studied the autolytic production of lactic acid by muscles for a period of forty to sixty minutes. In these circumstances the *production* of lactic acid by normal and by thyrotoxic muscles could be compared, and it was found that the lactic acid produced by thyrotoxic muscles

[1] This investigation was financed in part by a grant from the Bingham Fund.

was *less* than by normal muscles instead of greater as had been previously reported by Andrus and his coworkers.

If a decreased production of lactic acid by thyrotoxic muscles is admitted, the persistently high blood lactic acid frequently observed after exercise in patients suffering from Graves' disease has lost its obvious explanation. The idea was suggested by Buell, Strauss and Andrus (6) that this lacticacidemia both in Graves' disease and in Addison's disease (where similar relationships obtain) might be the result of a decreased rate of removal of lactic acid rather than an increased rate of its production. Since it is usually assumed that in warm-blooded animals the greater part of the lactic acid (which escapes oxidation to carbon dioxide and water) must be carried to the liver for synthesis to glycogen, it seemed logical to investigate the glycogenetic function of this organ in experimental hyperthyroidism. This has been done with the result that there are now experimental data to support the thesis that in this condition the liver has partially lost its ability readily to convert lactic acid into glycogen.

EXPERIMENTAL

Choice of method

The study of the conversion of the products of intermediary metabolism into liver glycogen presents many technical difficulties. Different methods of approach have been used such as (1) comparison of the composition of the liver of a large animal before and after certain experimental procedures, (2) comparison of the composition of the afferent and efferent blood of the liver of an experimentally treated large animal, (3) comparison of the chemical composition of the livers of a large group of experimentally treated small animals with a similar group of controls. For the present investigation the third method of approach was chosen because of the opportunity afforded for adequate control of conditions, since it is a well known fact that the glycogen and lactic acid content of tissues in general and of the liver in particular are subject to rapid change as the result of any one of many stimuli.

Cori and Cori (7) have studied by this method the fate of injected d. lactic acid under standardized conditions in the normal rat. They

found that d. lactic acid was converted rapidly into liver glycogen in contrast to l. lactic acid, which was converted only slowly. In the experiments to be reported the technique and conditions described by Cori and Cori were followed. The fate of standard amounts of d. lactic acid when injected by stomach tube into normal and also into thyroxinized young male rats was compared with control experiments in which physiological saline was given to similar animals. Thus the data afford several sets of contrasts (1) saline-fed normal animals with lactate-fed normal animals, (2) saline-fed thyroxinized animals with lactate-fed thyroxinized animals, (3) normal animals with thyroxinized animals, both saline-fed, and (4) normal animals with thyroxinized animals, both lactate-fed.

Young growing male rats of approximately 150 grams weight were chosen as experimental animals because of their general suitability and also because certain data with rats were available for comparison.

Procedure

Rats were rendered severely thyrotoxic by the repeated intramuscular injections on alternate days of a freshly prepared solution of synthetic thyroxine. The usual dose was 0.8 mg. thyroxine per 100 grams body weight, and the usual duration of the treatment was fourteen days (seven injections). Basal metabolic rates were not determined, but the degree of thyroxinization was severe as judged by loss of weight, appearance of the animals, the liver glycogen content, and blood sugar values.

When ready for use the animals were fasted for twenty-four hours and were then given by stomach tube 170 mg. d. lactic acid per 100 grams body weight. The lactic acid was prepared by the continuous ether extraction of an acidified solution of the zinc salt of d. lactic acid which was obtained from Prof. W. H. Peterson of the University of Wisconsin ($[\alpha]_{20}^{D} = -8.25$). The concentrated aqueous solution of lactic acid was brought to a pH of 7 with sodium hydroxide in order that the acid-base relationship might not be disturbed. Similar volumes of physiological saline solution were given to the control groups of animals.

After the stomach tube was withdrawn each animal was put into a separate metabolism cage with access to water but not to food. At

the end of three hours the animal was given sodium amytal intraperitoneally. The manipulation of the animal was carried out with extreme care so that the tissues analysed might represent as nearly as possible resting *in vivo* conditions, and that a uniform effect of the experimental procedure might be obtained on control and experimental animals alike. Five minutes after anesthesia was complete the gastrocnemii were rapidly dissected out and were immediately placed in tared tubes containing potassium hydroxide for glycogen determinations and iced trichloracetic acid for hexose phosphate estimations. The head was cut off and two ml. of blood were collected and precipitated immediately with tungstic acid for lactic acid and sugar determinations. The entire liver was rapidly extirpated and introduced into a tared tube containing potassium hydroxide for glycogen determinations. The alimentary tract was then tied at each end, dissected out, minced, and extracted three times with boiling water for lactic acid determinations. Finally, the urine remaining in the bladder was expressed and lactic acid was determined on aliquots of the total volume representing the experimental period.

The chemical methods employed were as follows: for glycogen the modification of the Pflüger method described by Good, Kramer, and Somogyi (8); for lactic acid the method of Friedemann and Kendall (9) with West's (10) improved apparatus; for Embden ester, the method of Cori and Cori (11); for sugar the 1929 modification of the Folin-Wu method (12).

Results

The results reported in tables 1 and 2 were obtained by averaging the individual values found in each group of animals. Although there were large variations in certain instances, as was to be expected, among individual animals in a given group, in no case did the significant results with individuals in one group overlap those obtained in a contrasting group. Consequently group averages may be used with confidence and are more significant than individual experiments.

In no case, even in the thyroxinized animals fed lactic acid, was there any appreciable amount of lactic acid found in the urine. The lactic acid absorbed was calculated as the difference between the amount given and the amount which remained in the alimentary

tract at the end of the experiment. In table 3, a carbohydrate balance has been calculated with the use of the data in tables 1 and 2 and also certain assumptions, namely, (1) that the blood glucose and blood lactic acid are distributed in one-half of the body weight, (2) that the muscles constitute one-half of the body weight and (3) that the liver

TABLE 1

Absorption of lactic acid

GROUP NUMBER	CONDITION	SUBSTANCE FED	NUMBER OF ANIMALS	AVERAGE BODY WEIGHT	LACTIC ACID GIVEN	INTESTINAL LACTIC ACID	URINARY LACTIC ACID	LACTIC ACID ABSORBED	
								Per animal	Per 100 grams body weight
				grams	*mgm.*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
1	Normal	Saline	9	144	0	3	0.3	0	0
2	Normal	D. lactic acid	11	141	240	88	0.9	152	108
3	Thyroxinized	Saline	10	177	0	3	0.3	0	0
4	Thyroxinized	D. lactic acid	14	159	301	90	1.3	210	132

TABLE 2

Analysis of tissues

GROUP NUMBER	CONDITION	SUBSTANCE FED	LIVER GLYCOGEN	BLOOD LACTIC ACID	BLOOD SUGAR	MUSCLE GLYCOGEN	EMBDEN ESTER (HEXOSE PHOSPHATE)
			mgm. per cent	*mgm. per cent*	*mgm. per cent*	*mgm. per cent*	*hexose, mgm. per cent*
1	Normal	Saline	390	18	138	490	56
2	Normal	D. lactic acid	1,570	26	165	530	70
3	Thyroxinized	Saline	100	17	107	410	59
4	Thyroxinized	D. lactic acid	420	39	138	490	84

constitutes three per cent of the body weight (13). Obviously, with a calculation of this type small differences can not be interpreted.

Only those results have been reported (44 animals) which were obtained after the experimental procedure was thoroughly standardized, and no selection of data has been made. Actually twice as many animals were used as were reported, in a vain attempt to introduce the lactic acid in a different manner, such as intraperitoneally

or intravenously. These procedures were eventually abandoned as being unsatisfactory.

DISCUSSION

The lactic acid absorbed by normal rats agreed well with the value found by the Coris (7). The apparent value, per 100 grams body weight, was somewhat higher in the thyroxinized animals. This

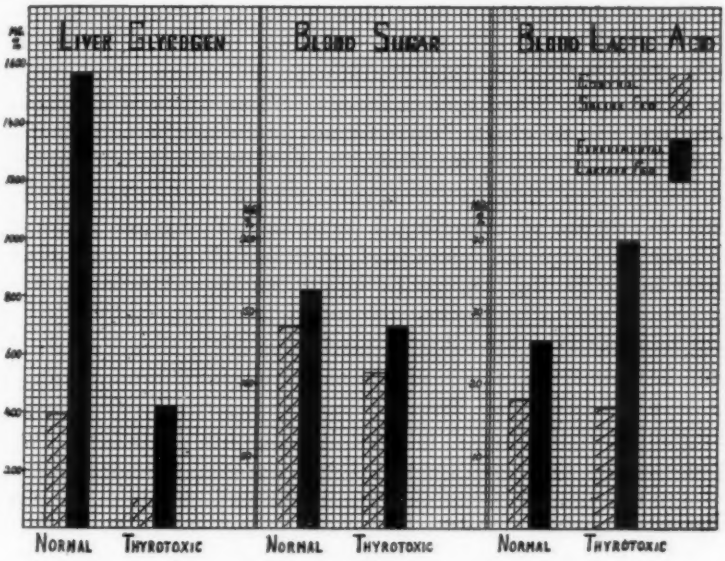

CHART 1

difference in the lactic acid absorbed largely disappears if the weight before thyroxinization is used as a basis of calculation. In the comparison between normal and thyrotoxic tissues consideration must be given to the fact that the muscles of thyroxinized animals have lost water and possibly other constituents such as fat.

The increase in liver glycogen attributable to lactate feeding was large in normal rats. The important observation is the fact that the rise in liver glycogen attributable to lactate feeding in the thyroxinized animals is only twenty-seven per cent of the rise in normal animals. This fact is strikingly demonstrated in the graph.

The amount of glycogen found at any one time in the liver must be the resultant of two principal factors: namely, (1) the rate at which glycogen is synthesized (in this instance from lactic acid) and (2) the rate at which glycogen is broken down into glucose. The synthesis of glycogen from lactic acid must be accompanied by a fall in blood and tissue lactic acid; the breakdown of glycogen into glucose must be accompanied by a rise in blood and tissue sugar.

Thus we see that at the end of three hours the thyroxinized lactate-fed rats had a higher blood lactic acid than the normal lactate-fed rats, although the level of blood lactic acid was the same in both groups of animals which had been saline-fed. These relations are shown graphically in the chart. These figures, in conjunction with the low liver glycogen of the thyroxinized animals, lend experimental support to the hypothesis that in severe hyperthyroidism the liver has partially lost its function of converting d. lactic acid readily into glycogen. All the data reported represented conditions obtaining three hours after lactate feeding. It may be argued that the sudden demand for oxygen produced by flooding the system with lactic acid makes a greater demand on the oxidative mechanism of the thyroxinized animal because of its extra load due to the increased basal metabolic rate in this condition. However, in these experiments there was a long interval (three hours), between the time when the lactic acid was given and the time when the animal was sacrificed, for determination of the distribution of carbohydrate in the various tissues. Consequently, any effect of sudden lack of oxygen was obviated.

As to the second factor influencing the glycogen content of the liver, namely, the rate of glycolysis, the evidence is difficult to interpret conclusively. Within the limits of experimental error the rise in blood sugar (31 mg. per cent) in the thyroxinized animal after lactate feeding was the same as in the normal animal after lactate feeding (27 mg. per cent). Certainly this observation does not support the hypothesis that the rate of glycolysis in the liver of an hyperthyroid individual is significantly increased. It is recognized, however, that this type of negative evidence does not constitute proof because of the physiological significance, in a rapidly circulating medium such as blood, of such amounts of a constituent as are insignificant analytically. There are also physiological factors such as possible dehydra-

tion which make exact interpretations difficult. Another line of evidence is afforded by these experiments, namely, that in the normal saline-fed animals and in the thyroxinized lactate-fed animals, the liver glycogens and the blood sugars of both groups had the same values. If glycolysis were proceeding at a more rapid rate in the thyroxinized animal, that fact presumably would have been illustrated by higher blood-sugar values.

From the carbohydrate balance in table 3 the interesting fact emerges that the same quantity (89 and 90 mg.) of lactic acid was accounted for in terms of carbohydrate in both normal and thyrotoxic animals. These figures were obtained by subtraction of the total carbohydrate of the 100 gram saline-fed animal from the total carbohydrate of the 100 gram lactate-fed animal. Actually the lactic acid absorbed per 100-gram rat, as previously discussed, was greater by the thyroxinized animals than by the normal animals. Consequently, the percentage recovery is somewhat less for the thyroxinized animals than for the normal. This is to be expected in view of the greater concentration of actively functioning cells in certain tissues of the thyroxinized animals and the increased basal metabolic rate in this condition.

TABLE 3

Carbohydrate balance (per 100 gram rat)

GROUP NUMBER	CONDITION	SUBSTANCE FED	TOTAL SUGAR	TOTAL LACTIC ACID	MUSCLE GLYCOGEN	LIVER GLYCOGEN	ESTER HEXOSE PHOSPHATE	TOTAL CARBOHYDRATE	INCREMENT	PER CENT RECOVERY
			mgm.	*mgm.*	*mgm.*	*mgm.*	*mgm. hexose*	*mgm.*	*mgm.*	
1	Normal	Saline	69	9	245	12	28	363		
2	Normal	D. lactic acid	83	13	265	57	35	453	90	83
3	Thyroxinized	Saline	54	8	205	3	30	300		
4	Thyroxinized	D. lactic acid	69	20	245	13	42	389	89	67

The possibility that the muscles may have played some part in the direct conversion of lactic acid into glycogen can not be definitely excluded, although it is usually assumed that in warm-blooded animals the lactic acid formed by the muscles must be carried to the liver for synthesis into glycogen.

CONCLUSION

Experimental data have been presented to support the hypothesis of Buell, Strauss and Andrus that in severe experimental hyperthyroidism the liver does not convert lactic acid into glycogen as readily as it does in normal individuals.

BIBLIOGRAPHY

(1) ANDRUS, E. C., AND MCEACHERN, D.: *Am. J. Med. Sc.*, **183**, 741 (1932).
(2) ANDRUS, E. C.: *Bull. Johns Hopkins Hosp.*, **50**, 383 (1932).
(3) *Idem: Am. Heart J.*, **8**, 66 (1932).
(4) *Idem: Trans. Ass. Am. Phys.*, **47**, 47 (1932).
(5) ANDRUS, E. C., MCEACHERN, D., PERLZWEIG, W. A., AND HERMAN, S.: *J. Clin. Inves.*, **9**, 16 (1930–31).
(6) BUELL, M. V., STRAUSS, M. B., AND ANDRUS, E. C.: *J. Biol. Chem.*, **98**, 645 (1932).
(7) CORI, C. F., AND CORI, G. T.: *Ibid.*, **81**, 389 (1929).
(8) GOOD, C. A., KRAMER, H., AND SOMOGYI, M.: *Ibid.*, **100**, 485 (1933).
(9) FRIEDEMANN, T. E., AND KENDALL, A. I.: *Ibid.*, **82**, 23 (1929).
(10) WEST, E. S.: *Ibid.*, **92**, 483 (1931).
(11) CORI, G. T., AND CORI, C. F.: *Ibid.*, **94**, 561 (1931–32).
(12) FOLIN, O., *Ibid.*, **82**, 91 (1929).
(13) CORI, C. F.: *Physiological Reviews*, **11**, 151 (1931).

AN EOSIN-METHYLENE-BLUE TECHNIQUE FOR RAPID TISSUE DIAGNOSIS

EDWARD STEPHEN STAFFORD, M.D.

From the Department of Surgery, The Johns Hopkins University

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Since Wilson (1) brought out his original method for the rapid diagnosis of tissue from the operating room, there have been many contributions to this subject. With the exception of the recently developed method of Terry (2), who uses free-hand razor sections, the usual custom has been to cut sections with a freezing microtome. The stains commonly employed have been methylene blue, or hematoxylin and eosin in various forms. The criticism of Wilson's method, and also of Broders' (3) recent modification of it, is that the sections rapidly lose their clearness and definition, and are not permanent. To overcome this, other techniques, using hematoxylin and eosin followed by a clearing and dehydrating fluid, such as that of Guttman (4) and that of Chase (5) have been developed. Hematoxylin, however, is not a consistently good stain for fresh or poorly fixed tissue. Geschichter (6) used complicated and expensive reagents. MacCarty (7) has correctly said that the stain does not make the diagnosis. The appearance, however, of sections of tissue prepared by the usual rapid method differs markedly from that of tissue carefully and slowly prepared in the routine way.

There are certain features essential to the success of any rapid technique. The method must consume a minimum of time, and must produce a section in which the cells are clear and well defined. Other features are desirable, such as permanency of the preparations and economy in the material used. In addition, the method should be simple and the finished section should be comparable in appearance to a stained paraffin section, thereby eliminating confusion and the need for specialization in this work. With this in mind, the method about to be described was developed.

Reagents

(1) Fixing solution:

15 per cent Formalin	75 cc.
Absolute alcohol	25 cc.

(2) Eosin solution:

Eosin	1 gram
Potassium bichromate	1 gram
Water	100 cc.

(3) Methylene-blue solution (Goodpasture):

Methylene blue	1 gram
Potassium carbonate	1 gram

Water..... 400 cc.

Boil 30 minutes, add 3 cc. of glacial acetic acid, shake until precipitate dissolves, and concentrate to volume of 200 cc.

(4) Dehydrating solution:

Absolute alcohol	1 part
Acetone	5 parts

(5) Xylol.....

(6) Canada Balsam.....

Method

(1) Cut small thin blocks (not over 3 mm. thick)
(2) Heat to boiling in fixing solution (use crucible or test-tube)
(3) Freeze and cut sections (first washing block in water)
(4) Stain 1 second in eosin solution
(5) Wash in water
(6) Stain deeply in methylene-blue solution (10 to 20 seconds)
(7) Wash in water
(8) Mount on slide
(9) Blot (use blotting-paper moistened with drop of dehydrating fluid)
(10) Dehydrate with dehydrating solution (15–20 drops)
(11) Dip slide into Xylol
(12) Mount in Canada Balsam

It was found that fixation was necessary in order to produce uniform staining of all types of tissue with the reagents used in this method. The fixation, in addition, rendered the actual cutting of sections much easier. The method of freezing the tissue and cutting the sections differs in no essential way from that described by Wilson, Broders *et al.* Small staining dishes are used, and the sections transferred with a glass hook. The sections, after being mounted on a slide, adhere to the slide and not to the blotting-paper, if the blotting-paper has been previously moistened. The eosin and methylene blue solutions described have been found more satisfactory than those used by Mallory (8). Since methylene blue is soluble in eosin, the eosin stain must be applied first. Both the eosin and the methylene blue solutions keep indefinitely, requiring only occasional filtering. They are ready for use as soon as made up. Acetone proved to be a very satisfactory dehydrating agent, and also dissolves the excess of eosin. In the small amounts used, it does not become an expensive item. This method has been in use in the surgical pathological laboratory of the Johns Hopkins Hospital for one year, and none of the preparations have faded or have lost definition. The coloring and appearance of the sections are sufficiently similar to those of paraffin hematoxylin—eosin sections to eliminate any confusion regarding cell morphology. Methylene blue has the advantage that it stains mast cells, bacteria, and neuroglia fibers.

In some of the methods mentioned above a preparation can be made in one minute or less. In the present method the average time consumed is 5 to 7 minutes. The disadvantage of this additional time seemed heavily outweighed by the increased facility of diagnosis offered by sections so prepared.

BIBLIOGRAPHY

(1) WILSON, L. B., 1905. A method for the rapid preparation of tissue for the microscope. *J. Am. Med. Assn.*, Vol. 45, p. 1737.

(2) TERRY, B. T., 1930. Rapid diagnosis of malignant tumors. *Texas State J. Med.*, Vol. 26, p. 434.

(3) BRODERS, A. C., 1931. Modification of Wilson's fresh frozen section technique. *J. Lab. and Clin. Med.*, Vol. 16, p. 734.

(4) GUTTMAN, P. H., 1932. Rapid method for frozen sections. *Arch. Path.*, Vol. 13, p. 433.

(5) CHASE, W. H., 1929. Rapid frozen section method for fresh tissue. *J. Techn. Methods.* Vol. 12, p. 126.

(6) GESCHICHTER, C. F., 1931. New stains in tissue diagnosis. *Am. J. Cancer (Suppt.)*. Vol. 15, p. 2169.

(7) MACCARTY, W. C., 1929. Diagnostic reliability of frozen sections. *Am. J. Path.*, Vol. 5, p. 377.

(8) MALLORY, F. B., AND WRIGHT, J. H., 1921. Pathological Technique. Seventh edition, Philadelphia.

THE TREATMENT OF SO-CALLED PSEUDO-MÉNIÈRE'S DISEASE

WALTER E. DANDY

The difference between the classical syndrome of Ménière's disease and so-called pseudo-Ménière's disease lies solely in the tests for hearing. In the former there is always an unilateral subtotal loss of hearing without which the diagnosis of Ménière's disease cannot be made: In pseudo-Ménière's disease the attacks of dizziness and the character of the dizziness are precisely similar, but there is no unilateral symptom or objective change in hearing by which the dizziness can be localized to one side.[1] From the standpoint of treatment this localizing distinction is all important, for Ménière's disease can be cured by sectioning the auditory nerve on the side known to be affected; whereas, in pseudo-Ménière's disease there is no indication by any objective test (or by subjective sensations) which auditory nerve is at fault, if indeed the fault lies in the nerve. In dividing the auditory nerve for Ménière's disease the loss of the remaining hearing was of relatively little importance, but one would never be willing to destroy normal hearing on one side (in pseudo-Ménière's disease) unless there was positive assurance that the attacks could be cured; and this, of course, is impossible. The recent substitution of hemisection of the auditory nerve in Ménière's disease, i.e., total section of the vestibular branch with preservation of the auditory branch and its function of hearing, has appeared to offer a solution of this difficulty. At the present time the latter procedure appears to abolish the attacks with equal certainty. Moreover, the fact that a large part of the cochlear branch of the nerve (nine-tenths in one case and more in another) can be sectioned without

[1] In a recent communication (Archives of Otolaryngology, July, 1934) I have expressed the belief and some evidence in support, that Ménière's disease and pseudo-Ménière's disease were really the same. At least, in many instances the unilateral alteration in hearing came months or years after the patient had been prostrated by the attacks, which in the beginning would have been classified under pseudo-Ménière's disease.

any appreciable (to the patient) loss of hearing has offered an additional margin of safety in proposing section of the vestibular branch of both auditory nerves[2] as a rational treatment for the cure of so-called pseudo-Ménière's attacks. The following case report, at least, shows that the operative procedure is possible and the immediate results in terms of dizziness suggest the probability of a cure. However, the latter hope cannot be claimed until time has passed final judgment. The physiological effects, or rather their absence in large part, are, at least, now determinable and are of interest. The following case is presented largely because it is essentially a human experiment in which the effects of sudden total ablation of the vestibular function of both sides can be studied.

Case. J. B., male, aged 44 years. Occupation, structural steel worker.

Complaint. Constant dizziness and dizzy attacks.

Family history is negative.

Past history. Despite the fact that ten months and a half before admission to the Johns Hopkins Hospital patient had been rejected for life insurance by three companies because he was found to have hypertension, there had been no symptoms of any kind.

Present illness. On December 6, 1933, seven and a half months before admission, patient had gone to bed after a day's work feeling as well as usual. Upon turning quickly from the right to the left side there immediately followed a very severe attack of vertigo in which objects whirled and ran together. Fifteen minutes later he began to vomit and this continued for twelve hours. He had a violent left-sided headache during the next day. During the next four weeks there was constant vertigo, but at a lower level and without acute exacerbations. During this time he remained in bed. His blood pressure which had been running around 180 dropped to 140 during this period. To him there seemed no relationship between his blood pressure and his vertigo. There was some buzzing in both ears; this was increased when the vertigo was more intense. When walking on the street he says he has a tendency to deviate toward the left, but at times it is to the right also. When turning the head sharply to the left the vertigo, which has been constant, is at once increased. He has since had several acute attacks of dizziness superimposed upon the more or less constant state of dizziness and always intensified by turning the head to the left. He says that tinnitus has been present off and on for a year and a half, but it caused no concern. He also complained of some blurring of vision.

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[2] Both vestibular nerves have just been sectioned in a case of bilateral Ménière's disease.

Physical and neurological examinations. Patient is a sparely nourished man, aged 44 years. He appears depressed and admits that his situation seems hopeless. He says he has always worked hard and is eager to do so now, but he sees no possibility of taking care of his family in the future. The physical examination

FIG. 1

reveals but one positive finding, namely, a hypertension which varies between 138/100 and 180/120.

The positive findings on neurological examination are: slight nystagmus on looking to either side; a suggestive Romberg; perhaps a slight tendency to stagger, although neither of the two latter findings is constant. At one time a slight ataxia

was noted when the finger-to-nose test was made, but at another time this test was negative. All the deep reflexes were normal. X-ray of the head was negative. Wassermann reaction from the blood was negative. The audiometer test (Fig. 2) showed 3 per cent loss of hearing on the right and 9 per cent loss on the left. From the caloric test patient became quite dizzy when either ear was irrigated with cold water; there was intensification of nystagmus of both sides.

Diagnosis. One could only make a diagnosis of pseudo-Ménière's disease because there was no marked loss of hearing on either side, and because tinnitus was not referred to either ear. Nor was there any discomfort in the region of either ear, such as so frequently obtains in Ménière's disease.

Operation. On July 2, 1934 a unilateral cerebellar approach was made first on the right, then on the left side (Fig. 1). The anterior five-eighths of each auditory

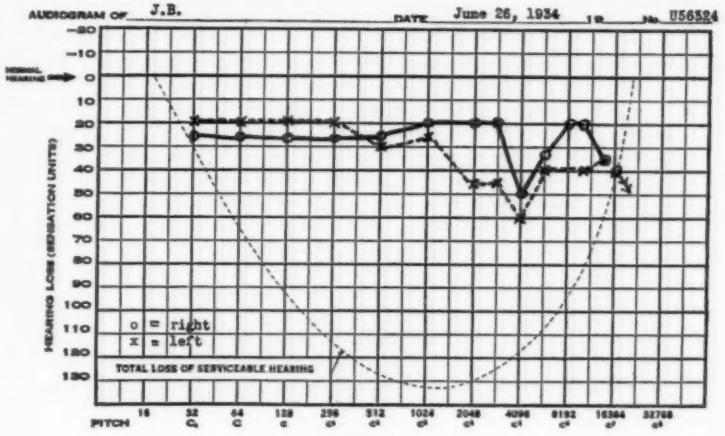

FIG. 2

nerve was divided. Section of this degree was expected to insure the loss of all vestibular fibers on each side and to leave three-eighths of the auditory nerve to retain unimpaired hearing. No bleeding or other difficulties were encountered throughout the operation.

Postoperative. July 2, 1934 (day of operation), 8:00 p.m. Patient says he has no dizziness whatever but has a new and unpleasant sensation. He doesn't know the exact position of his head and feels as though it is shaking from side to side when he attempts to move it. He is surprised when told that the head is perfectly steady. There is no rotation of objects. Diplopia is noted but there is no extraocular palsy. Nystagmus is present in both directions. His hearing appears to be unaffected. Nausea and vomiting are rather severe and are induced or intensified by moving the head.

July 3, 1934—day following operation. Symptoms are practically unchanged. No dizziness. He still feels as though his head was turning when he moved and even when at rest. Nausea, vomiting and diplopia persist.

July 6, 1934—5 days after operation. There has not been the slightest suggestion of the old dizziness at any time. Nausea and vomiting have ceased. Feeling of wobbling of head continues. There is no ataxia, nor has there been at any time since the operation.

July 8, 1934—7 days after operation. The "wobbling feeling" of the head is much improved.

July 11, 1934—9 days after operation. Sitting up in a chair. Says the wobbling sensation is improved, but he is uncertain about the exact position of the head

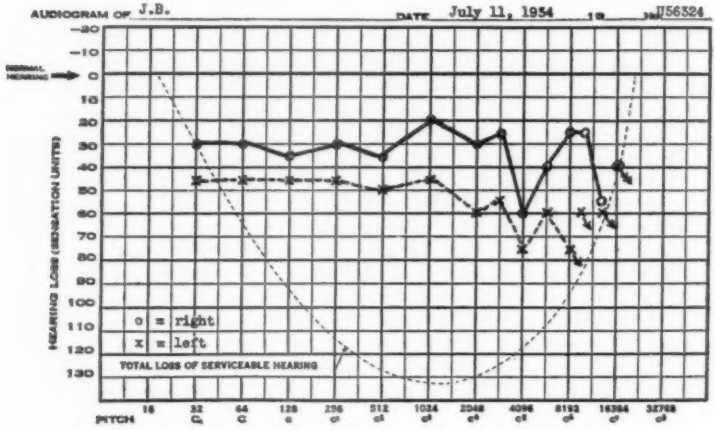

FIG. 3

and even more of the feet. Has the sensation that the feet continue turning after he moves them. Diplopia and nystagmus persist. The tinnitus has ceased. *Audiometer test* made today; hearing is not greatly changed (see chart (Fig. 3)). The *caloric test* shows no effect whatever of irrigations of hot and cold water.

July 12, 1934—11 days after operation. Walking. Takes short steps with a rather wide base. Walks a straight line and is quite steady. He says his feet feel as though they were whirling around, but the "wobbling sensation" of the head is nearly gone. Romberg test is negative. Still a little diplopia and nystagmus; no ataxia.

Another audiometer test was made today (Fig. 4).

Turning tests were made to both sides with the head erect and bent forward. Not the slightest suggestion of dizziness resulted.

July 19, 1934—17 days after operation. Discharged.

Discharge note. When asked if he had had any trace of dizziness, says "positively not." His gait is steady, along a straight line and with no uncertainty or swerving to either side. The postoperative sensation that the head was turning after movement has almost disappeared; the sensation of the feet turning is now present only when he walks fast.

There has been no *tinnitus* since the operation.

On standing with the feet together and eyes closed (Romberg) there is a little unsteadiness but he does not fall. The Romberg test was positive before operation, but the slight degree of unsteadiness now existing is probably about that obtaining at that time. Slight nystagmus persists when the eyes are turned to

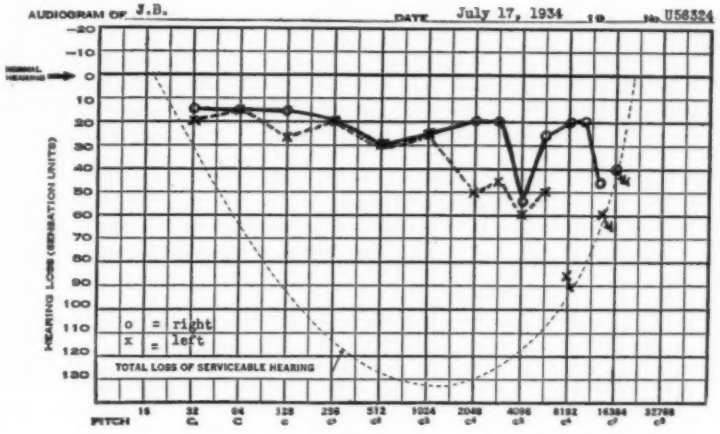

FIG. 4

either side. (It was present before the operation.) There is no ataxia. Diplopia has ceased. He has noticed no decrease from the preoperative level of hearing.

Patient was seen again July 27, 1934. He was still annoyed by the sensation that the position of his head and feet could not be accurately estimated and appeared to continue turning after movement. He says his gait is still uncertain, although, when tested, it does not appear abnormal, unless perhaps it may be a little cautious.

SUMMARY AND CONCLUSIONS

That the vestibular nerves are totally severed by the operation is shown by the following facts: (1) Irrigation of each ear with hot and cold water (Bárány test) provoked no nystagmus and induced no sub-

jective dizziness. (2) Whirling tests with the head bent forward produced no sign of dizziness, nor did the whirling cause any symptoms whatever. It would be interesting, indeed, to know whether this patient would be subject to seasickness.

That the hearing is practically unaffected is disclosed by comparing the postoperative and preoperative audiometer curves.

It is difficult to interpret the function of the semicircular canals from this deprivative experiment. One is amazed that almost no symptoms are induced by the abrupt loss of both semicircular canals in man. Objectively, absolutely nothing could be observed at any time. Subjectively the patient complained of a "wobbling" or turning feeling of the head upon movement and to some extent of the feet. This has, he says, no similarity whatever to dizziness with whirling objects. It appears to be more an inability to determine the exact position of his head and feet in space. It will be interesting to compare these symptoms with those of subsequent experiments of similar character. Nausea and vomiting were quite severe for a few days and perhaps are not unexpected, though it is difficult to interpret any particular relationship to the semicircular canals—perhaps no more than the diplopia which existed for ten days.

It is interesting that there was no effect whatever upon the so-called cerebellar signs, i.e., staggering gait, Romberg and ataxia.

That the state of constant dizziness which had persisted for nearly eight months, should have ceased immediately after the operation and have remained entirely absent for almost a month, at least, strongly suggests (one case over so short a time can hardly be accepted as proof) that dizziness is not possible after both vestibular nerves have been divided. In this connection it is interesting to compare the transient state of dizziness of varying degree that usually (but not always) obtains after section of one auditory nerve for Ménière's disease. On the other hand, when the function of a *normal* auditory nerve is suddenly destroyed there appears to be no post-operative dizziness.

If the above statements hold, the logical deductions would appear to be that: (1) Dizziness is due to a lesion (irritative or destructive) of some (doubtless any) part of the vestibular apparatus (nerve fibers and end organs). (2) That the sudden loss of one set of normal semi-

circular canals does not cause symptoms of abnormal function in the contralateral intact canals, i.e., does not cause dizziness. In other words, one set of normal semicircular canals is seemingly just as effective as two. The numerous acoustic tumors without dizziness also demonstrate this point. (3) That the transient postoperative dizziness that usually follows section of one auditory nerve for Ménière's disease is due to some (unknown) underlying pathological process responsible for Ménière's disease, and located in the central nervous pathways. It is obvious that all dizziness would instantly cease after the section of the auditory nerve, if the lesion were in the semicircular canals. (4) If the results in the case presented in this communication are obtained in others, and there is every reason to believe they will be, it would be possible to stop the rare instances of protracted postoperative dizziness that obtains after sectioning the auditory nerve for Ménière's disease.

BIBLIOGRAPHY

DANDY, W. E.: Ménière's disease. Its Diagnosis and a Method of Treatment. Archives of Surgery, 1928, xvi, 1127.

DANDY, W. E.: An analysis of 42 cases of Ménière's disease, Symptoms, Objective Findings and Treatment. Archives of Otolaryngology, July, 1934.

EFFECTS ON HEARING AFTER SUBTOTAL SECTION OF THE COCHLEAR BRANCH OF THE AUDITORY NERVE

WALTER E. DANDY

In earlier communications I have shown that if one-eighth or one-half of the cochlear branch of the auditory nerve was divided there was very little loss of hearing and any loss that occurred was strictly confined to the higher tones. This note concerns the physiological effect of still further operative reduction in size of this nerve in two patients. The effect can best be seen by comparing the audiometer curves before and after operation.

Case I was a white woman, aged 62 years, who was operated on May 4, 1934. It was estimated that one-eighth to one-tenth of the cochlear branch remained after subtotal division of the left auditory nerve for Ménière's disease. The extent of this division was made deliberately because after hemisection of the nerve there was a separate fasciculus and thinking it possibly a part of the vestibular branch subtotal section of the remaining part of the nerve was made to the degree mentioned.

It will be noted that in the audiometer tests taken after the operation there was loss of all of the high tones above pitch 1024 on the operated side (Figs. 1–3). However, these tones are of little practical use in hearing so that the patient was unable to detect any difference in her hearing. It will be noted that there is a marked improvement in the hearing on the operated side, and a marked drop in the hearing on the opposite or normal side which has not been operated upon. Neither of these changes can be significant and both would appear to represent merely normal differences that may obtain in an audiometer curve; certainly there is no reason for a drop in hearing on the unoperated side, and it is impossible to believe that there could be an actual improvement in the hearing on the operated side.

Although tinnitus had diminished, it was still present at the time these audiometer tests were made so that the change in hearing could hardly be dependent upon this source.

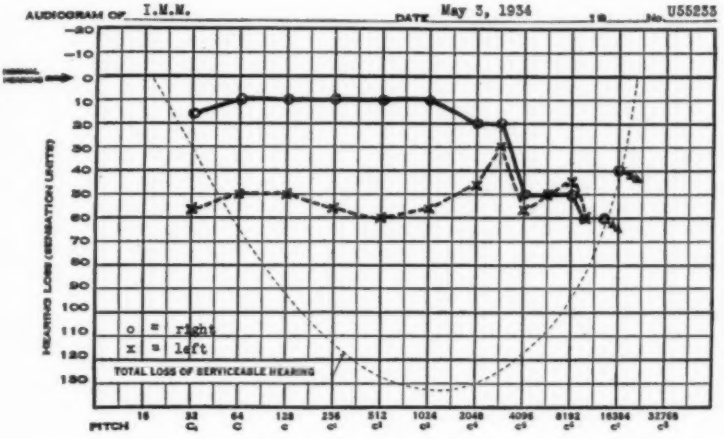

FIG. 1

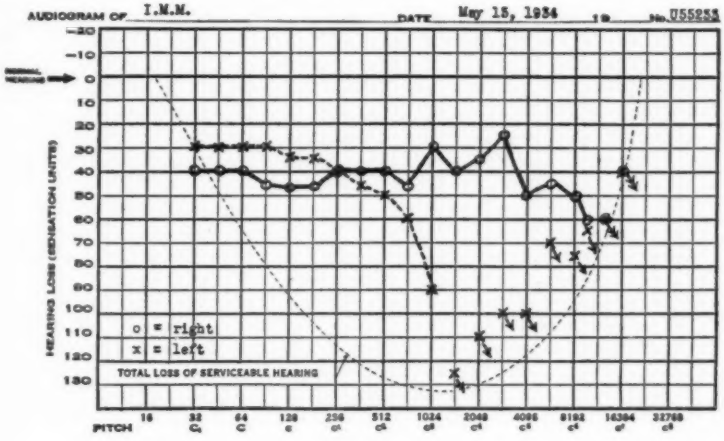

FIG. 2

Case II was a white man, aged 48 years. He was operated upon for Ménière's disease June 28, 1934. The auditory nerve ran an oblique course, and was surmounted by a small artery which, however, gave

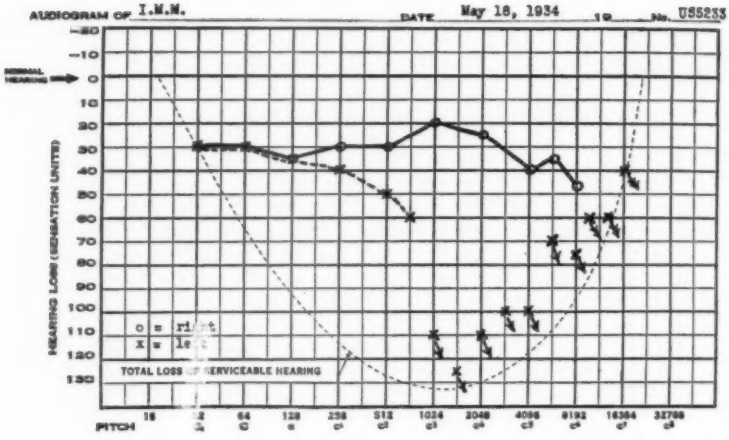

FIG. 3

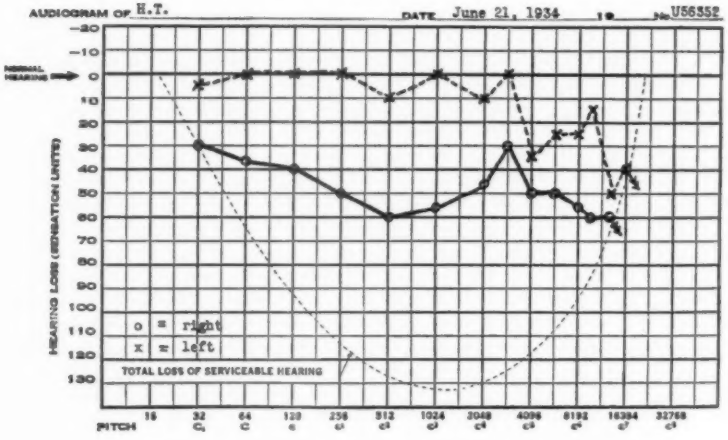

FIG. 4

no trouble. Because of the abnormal direction of the nerve, which appeared to be on a stretch, it was our plan to divide the entire nerve. However, a small filament estimated to be about one-eighth, or less, of the total volume of the cochlear branch remained.

The preoperative (Fig. 4) and postoperative (Fig. 5) audiometer curves are appended. We can detect no difference in these curves. Through this small filament, therefore, the hearing of all tones is conveyed. Why there should not be loss of high tones as in Case I, I have no explanation to offer.

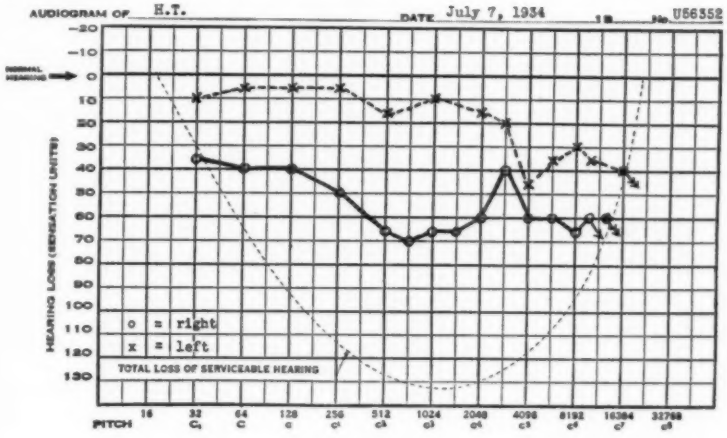

FIG. 5

COMMENT

From these two cases it is evident that one can sacrifice a very large portion of the auditory nerve and still retain normal, or nearly normal hearing. Any loss which may occur is only in the high tones, which are of no practical value in ordinary hearing. The results are essentially the same with the subtotal resection as when smaller amounts of the nerve are cut. The experiments on the auditory nerve are, therefore, quite similar to those of the trigeminal and optic nerves, in both of which a large volume of the nerve can be sacrificed without loss of function.

BIBLIOGRAPHY

DANDY, W. E.: Treatment of Ménière's disease by section of only the vestibular portion of the acoustic nerve. The Johns Hopkins Hospital Bulletin, 1933, liii, 52.

DANDY, W. E.: The effect of hemisection of the cochlear branch of the human auditory nerve. Preliminary report. The Johns Hopkins Hospital Bulletin, 1934, liv, 208.